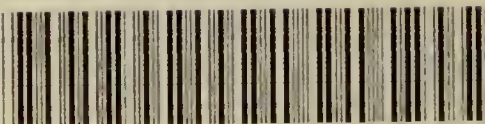


VACCINE THERAPY
ITS THEORY AND PRACTICE

R. W. ALLEN

FOURTH EDITION



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VACCINE THERAPY
ITS THEORY AND PRACTICE

*To Sir James Mackenzie
with best wishes from the author.*

VACCINE THERAPY

ITS THEORY AND PRACTICE

BY

R. W. ALLEN, M.D., B.S. (LOND.)

LATE CLINICAL PATHOLOGIST TO THE MOUNT VERNON HOSPITAL FOR DISEASE
OF THE CHEST; LATE PATHOLOGIST TO THE ROYAL EYE HOSPITAL;
LATE GULL STUDENT OF PATHOLOGY, GUY'S HOSPITAL

FOURTH EDITION

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PREFACE TO THE FOURTH EDITION

THE great developments and extensions which have been made in vaccine therapy since the appearance of the third edition in 1910 have appeared to justify the attempt of so altering the scheme of this work as to convert it into a systematic account of the applications of vaccine treatment to the bacterial diseases of the various parts of the body. This has necessitated a great enlargement and the complete rewriting of the book, but it is hoped that the sphere of its usefulness and the ease of reference will be thereby so increased as to afford ample recompense to the author for the labour incurred therein.

128, HARLEY STREET, W.

November, 1912.

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VACCINE THERAPY

INTRODUCTION

ONE of the most striking phenomena to which the attention of the student of bacterial diseases must perforce be attracted is the way in which certain individuals pass through life free from microbic invasion, whereas others are attacked, it may be from the cradle, by this or that bacterium. Why is it that one as an infant contracts a staphylococcal conjunctivitis, as a child is subject to recurrent furunculosis, as a youth to severe acne, and perhaps as an adult to a chronic eczema, whereas another throughout life is immune to all attacks by the staphylococcus? The tissues of the one appear to be suited to its growth, those of the other to be unsuited; but of the intrinsic cause of this difference in so-called 'immunity' we are in ignorance.

This difference in immunity may be local or it may be general. There has, for instance, just passed through my hands a patient resident in Guatemala. During the past five years epidemics of pneumonia have swept the city, usually twice a year. He has never contracted this disease, but has on each occasion been attacked by very severe nasal catarrhs, which have failed to spread down even to the larynx. Smears and cultures taken from the nasal mucosa show vast numbers of the pneumococcus,

and it would appear that the tissues of his nasal and post-nasal spaces are highly susceptible to the attacks of this organism, while those of the larynx, trachea, bronchi, and lungs, are highly resistant.

In the study of the question of immunity attention has been almost entirely concentrated upon the blood, to the exclusion of the subcutaneous and muscle tissues, and this I look on as a great mistake. The same blood supplies this man's nasal mucosa and pulmonary tissues, yet, as we have seen, the former are very vulnerable, the latter very invulnerable, to bacterial attacks. If immunity were dependent mainly on the protective substances carried by the blood-stream, this great difference should not exist. Very slight alterations in the chemical constitution of culture media greatly influence the rate of bacterial growth, very slight differences in the chemical composition of the soil in various parts of a field greatly affect the yield of crop, and on analogy I cannot but feel that the real reason why bacteria multiply in one tissue and not in another is that the chemical constitution of the soil is favourable in the first locality and unfavourable in the second. Accurate chemical and other observations upon the differences which exist between the tissues, say, of the lungs of individuals not affected by pulmonary tuberculosis, and of the affected and unaffected lungs of those who are, are much to be desired. Churchill many years ago declared that susceptibility to invasion by the tubercle bacillus was due to lack of organic phosphorus in the tissues. He was led, I believe, to this view by the observation that excess of phosphates are excreted in the urine in this disease, not by any accurate chemical analyses of the tissues. To remedy this defect, he introduced the hypophosphites into medicine; but while it is

admitted that they act as a powerful tonic, it does not appear that their use specifically renders the tissues of the user less vulnerable to the attacks of the tubercle bacillus.

That inorganic and simple chemical bodies are not without significance in bacterial diseases is evidenced by the effect of injections of isotonic sea-water and by the results of ionic medication upon various bacterial infections. The great retention of sodium chloride in the system which occurs in cases of pneumonia points in the same direction. Whether this retention is localized especially in the pulmonary tissues, and whether it is an attempt on Nature's part to render the soil unsuited to bacterial growth, I know not. Should observations show that there are intrinsic and specific differences of composition between infected and uninfected tissues, it will remain to learn whether the difference be the cause or the result of the infection, and to devise methods whereby the chemical composition may be modified locally as well as generally.

Too much attention has been directed to the study of the substances which kill off the bacteria which have gained a footing and are in process of multiplication, to the exclusion of the study of the factors which maintain resistance and preclude infection.

Immunity, as we have seen, may be local or general; it may also be complete or partial, natural or acquired.

The lower animals appear to be incapable of being infected by the gonococcus; their immunity is therefore said to be complete or absolute. The higher apes, although naturally never infected by syphilis, are yet capable in certain instances of being so infected artificially. Their immunity, though of a very high degree, is therefore partial, not absolute.

Natural immunity is the resisting power inherent in an individual independent of influences from without ; acquired immunity is the resisting power gained by an individual in consequence of influences from without. Natural immunity is frequently a characteristic common to all members of a species, as in the case of the immunity of the lower animals to the gonococcus ; but in some members of a species it may be less complete than in others.

In acquired immunity the protection is, as a rule, conferred on an individual by the processes whereby recovery is brought about from the attacks of that bacterium against which immunity has been acquired. This, again, may be complete or partial. For instance, when once a human being has recovered from the attacks of the infective agents responsible for the various acute infective fevers, such as scarlet fever or measles, he is in the great majority of cases entirely immune for the rest of life ; but in a small percentage of cases the acquired immunity is only partial, and a second attack may be incurred. Recovery from all infective diseases, then, is due to the acquirement of immunity, which may be partial or complete, local or general, and the question arises, Upon what does this acquired immunity depend ? It depends—at all events, in part—upon the elaboration within the tissues of various substances inimical to the bacteria and their products. To these substances the name of ‘immune’ or ‘anti’ bodies has been given. Some of these appear to be products of normal tissue activities, and therefore to be always present in less or greater amounts ; others are elaborated only in response to an infection, and are of service only against that particular bacterium in response to whose attacks they have been elaborated.

These are therefore known as 'specific' antibodies, the former as 'non-specific' antibodies.

Immune bodies are of various kinds, possessing different characteristics and performing different rôles. Among them are the following :

Antitoxins.—Specific bodies which neutralize the poisons elaborated within the tissues by a disease-producing micro-organism.

Agglutinins.—Specific or partly specific bodies which cause the corresponding bacilli to collect in clumps when suspended in a liquid medium.

Lysins.—Specific bodies which have the power of dissolving bacteria.

Opsonins.—Substances which have the power of combining with bacteria, and thereby rendering them more easily taken up by the phagocytic cells.

Whether non-specific opsonins exist, and how far opsonins are truly specific, are disputed points.

In vaccine therapy an attempt is made to exploit healthy tissues in the interest of diseased ones. The latter having failed to respond to infection by the elaboration of antibodies in quantities sufficient to overcome the infection, a stimulus is applied to the former by the introduction of killed cultures of the infecting microbe, in the hope that they may respond by the elaboration of antibodies and that the defect may thereby be made good at the infected focus.

Although no means have yet been devised for the direct estimation of any of these antibodies, in the case of some methods are available for making comparative observations. In the following pages we shall consider how this is done ; what variations are found in health and in infectious conditions which proceed to recovery, chronicity, or

death ; diseuss how their formation may be stimulated when defective and eontrolled when irregular or ill-adjusted ; and how this information is made use of in vaccine treatment, and with what results.

For a full exposition of the theories of immunity the reader is referred to Emery's 'Immunity and Speeific Therapy,' and to Bolduan's 'Immune Sera.'

CHAPTER I

THE ANTIBODIES: THEIR NATURE, SOURCE, AND FUNCTIONS

1. ANTITOXINS.

THE pathogenic action of bacteria appears to be almost entirely due to various poisonous substances or toxins which they elaborate within the host. These toxins are of various kinds. There are the true specific toxins, which are, as a rule, formed in but small amounts, are of complex chemical constitution, and possess extremely powerful properties; there are also the less important products of their metabolism, such as acids, alkalies, indol, nitrites, etc., which may be formed in considerable quantities, are of simple chemical constitution, are much less powerful than the true specific toxins, and, while possessing poisonous properties which may give rise to some of the symptoms of a disease, are not really concerned in the production of the disease. The acid or nitrite forming properties of a bacillus may be modified or even completely abolished without doing away with the power of that bacillus to originate its characteristic disease. Closely allied with the true toxins are three other products of bacterial growth—the leucolysins, the cytoly-sins, and the hæmolysins, which have the power of dissolving leucocytes, fixed tissue cells, and red blood-corpuscles respectively. It is to the formation of hæmolysins within the body that the anæmia characteristic of some bacterial invasions, such as that by the streptococcus, is to be attributed.

The true toxins may be divided into two groups—the extracellular, or ‘exotoxins,’ which are soluble, and are given off into a suitable culture medium; and the intracellular, or ‘endotoxins,’ which are insoluble, and are set free into the culture medium only on the death and disintegration of the bacilli.

Not all bacteria form ‘exotoxins.’ The most important ones which do are the *Bacillus tetanus*, *B. diphtheriæ*, and *B. botulinus*. Of these, the true specific toxins can be obtained in a comparatively pure and highly concentrated form.

The ‘endotoxins,’ which are probably the true specific toxins in the case of most bacteria, can only be obtained in a concentrated and approximately pure state from the bodies of the bacteria with great difficulty—best by the method of MacFadyen and Rowland, which consists in freezing with liquid air, grinding into a fine powder, extracting with normal saline, and centrifugalizing.

Function of Antitoxins.—When we consider that an animal immunized against the action of a toxin is also immune to the attacks of the bacterium from which that toxin is derived, and that it is theoretically possible to render an animal which is susceptible to any toxin immune to it by injecting that toxin in suitable doses at suitable intervals, it would appear—(1) that in the process of natural recovery from disease antitoxin formation must play a very important part; (2) that the introduction into the circulation of antitoxin in suitable doses would be an invaluable and infallible method of combating bacterial invasion.

With regard to the first of these suppositions, it, however, appears that antitoxin formation does not play by any means as important a part in recovery from disease

as might be imagined, for recovery is frequently well advanced before the presence of any antitoxin can be detected in the blood. For instance, even in diphtheria, where so much benefit has been found to accrue from injections of alien serum rich in antibodies, antitoxin has sometimes been found to be absent from the blood throughout the whole course of an attack, from which, nevertheless, good recovery is made. It is therefore obvious that toxins must be dealt with in ways other than by specific neutralization with circulating antitoxin. It has been found that they are excreted in small quantities in the urine, sweat, and fæces; but the chief rôle in their disposal is attributed to the leucocytes and various tissue cells, especially those of the liver and spleen. These combine with them, oxidizing and hydrolyzing them, and breaking them down into inert simple chemical compounds.

In some cases, however, antitoxin formation is of considerable importance. It is not certain what cells are concerned in its production, but it is highly probable that the leucocytes, especially the large mononuclear variety, function in this way. In certain acute infectious processes, such as pneumonia, it is well recognized that the prognosis is best when there is a high leucocytosis, not so good when there is a moderate one, and serious when there is no leucocytosis or a leucopenia. A connection between this and the rôle of the leucocytes in antitoxin formation is highly probable.

Since, then, we know that the artificial introduction into the tissues of suitable doses of antitoxin is highly beneficial, even in diseases from which good recovery may be made though little or no antitoxin is demonstrable in the blood; and, secondly, that antitoxin is sometimes of

considerable importance to recovery, it would appear logical to treat all cases of bacterial invasion either by stimulating antitoxin formation within the organism, and so producing an active specific immunity, or by the introduction from without of alien antitoxin in suitable doses—*i.e.*, by producing a 'passive' immunity.

Serious difficulties, however, present themselves. Firstly, we are ignorant of any means whereby the rapid production of 'active' antitoxic immunity can be stimulated. The introduction within the tissues of the small amounts of toxin contained in some vaccines may act in this direction, but this stimulus is a small one, and its administration infrequent. Secondly, it has been found possible only in a few instances to produce a serum with active antitoxic properties, whereby 'passive' antitoxic immunity may be secured. The cases in which this has been done are in regard to those bacteria which form 'exotoxins.' As we have seen, great difficulty has been experienced in obtaining potent preparations of 'endotoxin,' and inasmuch as substances other than endotoxin enter into such solutions, various other immune bodies are formed when these are used for the preparation of anti-endotoxic serum. It thus comes about that most antisera depend for their activity upon the presence of lysin or opsonin, while in some cases they may contain the actual bacterial bodies and act as vaccines.

Antisera may thus be divided into—

1. Those containing anti-exotoxin, and dependent on this for their therapeutic action, such as antidiphtheritic and antitetanic sera. These are devoid of bactericidal power, and accordingly play no part in the removal of the infective agent, this being then brought about by natural means which the body has at its command.

2. Those containing anti-endotoxin and other immune bodies, such as lysins and opsonins, but dependent chiefly on the anti-endotoxin for their therapeutic value, such as MacFadyen's antityphoid serum.

3. Those containing little or no antitoxin, and dependent for their activity on the lysin, opsonin, and other immune bodies which they contain, such as anticholera, antityphoid, antidysentery, antistreptococcic, antimeningococcic, antipneumococcic, and antigonococcic, sera.

• These sera are in general valuable for conferring protection, but are not always curative—indeed, their use during active disease may not be altogether free from danger. Thus the administration of anticholera or antityphoid serum, which each depend for their activity on the lysin they contain, may result in the extra-leucocytic lysis of so many bacteria that the resultant flooding of the tissues with large quantities of their contained endotoxin may imperil the life of the recipient from the additional toxæmia.

The causes of the disappointing results obtained with some of these antisera are complex, and for their explanation the reader is referred to special treatises on immunity.

2. AGGLUTININS.

The agglutination reaction was originally observed by Charrin and Roger in 1889 in the case of the *B. pyocyaneus*, but was first studied by Grüber and Durham in 1896, and was applied by them to the identification of bacteria. Later it was utilized by Widal in the diagnosis of the unknown organism causing a disease, and as this has become its most important use, the phenomenon is now often known as Widal's reaction

The reaction consists in this : If the serum of an animal immunized against a motile organism, such as the *Vibrio cholerae*, *B. pyocyaneus*, *B. typhosus*, or *Micrococcus melitensis*, be suitably diluted, and a drop of this be mixed with a drop of a uniform emulsion in normal salt solution of an eighteen hours' growth on agar of the bacillus to which immunity has been produced, and the mixture be observed in a hanging-drop preparation under the $\frac{1}{6}$ -inch objective of the microscope, it will be seen that pairs of the bacilli approach each other, revolve rapidly round an axis as if linked together, gradually lose their motility, and attract other bacilli to themselves. these in turn making violent motions as if to tear themselves away, which, however, soon cease. Fresh individuals are attracted, and the process continues until finally, at the end of thirty to sixty minutes, the bacilli, instead of being uniformly dispersed throughout the liquid, are aggregated together in clumps, the intervening fluid being almost bacteria free.

Although the reaction is best observed when young motile bacilli are employed, it is given with nearly all species of bacteria when mixed with the corresponding serum. Motility in the bacteria is not essential, and clumping occurs with dead bacteria almost as well as with living ones. The clumping and sedimentation of the agglutinated bacteria may also be observed macroscopically by the employment of Wright's sedimentation tubes (for full description of technique, see *British Medical Journal*, February 5, 1898).

The substance in the serum which causes the phenomenon is known as 'agglutinin,' and is supposed to act by producing an alteration in the surface tension between the bacteria and the fluid in which they lie.

The application of the reaction to diagnosis depends on the fact that agglutinins are highly specific bodies—in other words, the serum of an animal immunized against the *V. cholerae* will agglutinate an emulsion of that organism, but not one of the *B. typhosus*. The specificity is not, however, absolute, for it is found that closely allied bacteria may be clumped by the same serum belonging to an animal immunized against only one variety of the bacteria. For instance, a typhoid serum will clump the paratyphoid bacilli, the *B. coli*, and paracolon bacilli. The reaction will, however, be more marked with the *B. typhosus* than with any of the allied organisms.

For this reason, as well as owing to the fact that normal serum contains small quantities of agglutinin for most bacteria, the 'immune' serum is always diluted; and unless agglutination is produced definitely when, say, a twenty-fold dilution of the serum is employed, the reaction is not regarded as being positive.

In the case of the serum of a highly immunized animal, clumping may be obtained with dilutions of one hundred thousandfold or even one millionfold.

The method of applying the test by means of Wright's sedimentation tubes is as follows: Suppose that an infection of a patient by the *M. melitensis* is suspected. Samples of the patient's blood and of the blood of a normal person are taken, allowed to coagulate, and the sera collected. Of each serum a dilution of 1 part of serum to 9 parts of normal salt solution is made. This is known as a 1 in 10 dilution. In addition, dilutions of 1 in 25, 1 in 50, 1 in 100, 1 in 250, 1 in 500, 1 in 1,000, and higher ones, if desired, are made. A five to seven days' growth of a known stain of the *M. melitensis* on agar is then emulsified with normal salt solution, and centrifugal-

ized to remove all clumps. The upper portion, which should consist of a uniform emulsion of the organism, is pipetted off. Equal volumes of it and of each dilution of each serum are then mixed together in a series of sedimentation tubes of about 1 mm. in diameter, and allowed to stand at 37° C. or at room temperature, being examined after intervals of thirty and sixty minutes. It has been found that normal serum usually produces complete sedimentation of the *M. melitensis* in a dilution of 1 in 2, and a faint trace of agglutination only in a dilution of 1 in 10. If, therefore, the patient's serum is found to produce complete sedimentation, the bacilli being all collected at the bottom of the tube in firm clumps, and the supernatant liquid being perfectly clear in the dilution of 1 in 10, then the presence of excess of agglutinin towards the *M. melitensis* is demonstrated, and infection by that organism rendered probable. If clumping occurs in the higher dilutions, the probability is converted into a certainty.

In watching the formation of agglutinin during the course of a disease, determination has to be made of the highest dilution with which complete sedimentation occurs. Inasmuch as normal serum often clumps the *B. typhosus* in a 1 in 10 dilution, clumping with a dilution of 1 in 20 of the suspected serum is considered essential to the diagnosis of infection by that organism.

Nature of Agglutinins.—Agglutinins are fairly resistant to heat. Thus, their action is unimpaired by heating them to 60° C.; a temperature of 65° C. is, however, fatal. In this respect, as we shall see, they differ from the lysins. That agglutinins and lysins are distinct bodies is also proved by the fact that a serum may agglutinate strongly, but produce no lysis, and *vice versa*.

The Site of Formation of Agglutinins.—When a series of animals are inoculated with a dead culture of a given bacterium and killed at varying periods, and emulsions made of the various tissues, it is found that agglutinins first appear in the preparations made from the lymphoid tissues, red marrow, and spleen. It is therefore held that they are formed in these tissues, the cells responsible being the leucocytes, and chiefly those of the large mononuclear variety. Metchnikoff found that a peritoneal exudate might be richer in agglutinins than the blood, and considers that they arise from the endothelial cells and leucocytes.

The Function of Agglutinins in the Production of Immunity.—The fact that agglutinins are formed in response to very nearly all bacterial infections, and especially in the case of those due to motile bacilli, at once suggests that their function is to promote the destruction of the bacilli by annulling the motility and causing aggregation. Agglutinated bacteria are, however, capable of living and of reproducing themselves, and no microscopical change can be detected in their structure. So far, also, from promoting lysis, agglutinins appear to hinder it, the aggregation of the bacilli tending to shield them from the solvent action of the lysins. My own view is that agglutination is of service to the human body in this way: The clumped and immotile bacteria are more readily caught up in the various tissues, especially those of the liver, spleen, and lymphatic glands, where the various immune bodies are generated, and therefore present in the highest degree, and opportunity thereby afforded for lysis and phagocytosis to occur in the most favourable situations. So great may be the demand upon the various immune bodies in these situations that, as Wright has

shown in the case of the agglutinins for the *B. typhosus* and *M. melitensis* in the splenic serum of cases which have ended fatally, complete local exhaustion of the supply may be brought about.

The Course of Agglutinin Formation in Disease.—The formation of agglutinin follows the rule which appears to govern the elaboration of all immune bodies. After infection there is an immediate fall in their amount, which may continue and persist for two or three days; then there is a gradual recovery, which is succeeded by a rapid rise, occurring in Malta fever on the fourth or fifth day after the development of pyrexia, in typhoid fever on the seventh or eighth day, or even later. Maximum development is reached in Malta fever by the ninth to eleventh day, in typhoid fever by the end of the second week, and continues until convalescence is well established. Thereafter there is a fall, so very slow and steady that in Malta fever a reaction is usually obtained in a 1 in 250 dilution at the end of the first year, and in a 1 in 100 dilution at the end of the second year. By the end of the third year it has usually fallen to normal, but it has been observed in a 1 in 20 dilution even at the end of the seventh year.

Prognostic Use of the Agglutination Test.—Courmont, from a study of the agglutinins in a large series of cases of typhoid fever, concluded that in that disease—(1) a large development of agglutinin, especially if this be accompanied by fall of temperature, is invariably a good sign; (2) a small development, accompanied by rise of temperature, is always a bad sign; (3) strong agglutination throughout an attack is good, whereas weak agglutination is bad, as this is usually found either in slight attacks which tend to relapse or in very severe cases.

Wright found that cases might be tabulated prognostically as follows in Malta fever :

Bad prognosis : cases of a severe type clinically, with persistent low agglutinin development ; also when in severe cases there is a rapid fall from a high to a low level.

Good prognosis, when the agglutinin curve maintains a constant high level well into convalescence.

Guarded prognosis, when a high agglutination value considerably decreases, despite the clinical features remaining not unsatisfactory, as this indicates the probability of a long convalescence, and perhaps relapses. If the fall be rapid, a relapse within a day or two is highly probable.

It thus appears that the course of the agglutination curve in these, and perhaps in some other diseases, affords a valuable indication of the progress of immunity. It therefore follows that either agglutinins themselves are of value in immunity, or that the curve of their production runs more or less parallel with the curves of the other immune bodies, upon the elaboration of which recovery depends. Both alternatives are possible, and this would appear to be a reasonable view to adopt. Inasmuch, therefore, as the estimation of lysin is a laborious task, and that of opsonin sometimes presents peculiar difficulties, guidance as to the progress of immunization may therefore at times be sought in the more easily determined agglutinin curve.

3. LYSINS.

Demonstration of Lysin.—Pfeiffer observed that when cholera vibrios were injected into the peritoneal cavity of a guinea-pig which had been highly immunized against this

organism, they were first deprived of motility, then lost their shape, being converted into spherical masses which stained badly, became smaller and smaller, and finally disappeared. The same phenomenon may be observed *in vitro* by adding the serum of an animal immunized against the cholera vibrio, typhoid or colon bacillus, to an emulsion of a culture of the corresponding bacterium.

Nature of Lysin.—The interaction of two substances has been found necessary for the reaction, the one fairly resistant to heat—*i.e.*, ‘thermostable’—and occurring in appreciable amount in the serum of immunized animals only; the other destroyed by heating to 55° C. for thirty minutes—*i.e.*, ‘thermolabile’—and occurring in the serum both of normal and of immunized animals. The former of these is known as the ‘immune body,’ or ‘amboceptor,’ and its combination with the bacteria is necessary before union with the thermolabile body, which is known as ‘alexin,’ or ‘complement,’ can occur and lysis result.

Source of Lysin.—The source of the alexin or complement is a matter of dispute. It appears to be absent, or almost absent, from the blood-plasma, and to be set free when coagulation occurs. One of its sources is therefore held to be the polymorphonuclear leucocytes. The objection has been urged to this that it is difficult to assume that the bactericidal power of the serum is only a particular manifestation of a digestive power originally resident in the leucocyte when it is realized that the serum exerts a bactericidal action only on certain varieties of bacteria, whereas the leucocytes exert a digestive action on bacteria generally. The recent work of Zinnsch,¹ how-

¹ *Journal of Medical Research*, June, 1910, p. 397.

ever, clearly shows that while normal leucocytes do contain bactericidal substances, these are of a different nature to those in the serum, a temperature of 75° C. being necessary for their destruction. The amount of this substance which they contain is insignificant in amount to that of the lysin in the serum, and cannot, apparently, be increased by artificial immunization, as the serum lysin can be. Ehrlich, on quite inadequate evidence, attributes the function of lysin formation to the liver cells.

The 'amboceptor,' or 'immune body,' is formed in the lymphoid tissues, and is probably secreted by the mononuclear leucocytes. It circulates as such, coagulation not being necessary for its appearance.

Lysins in Normal Serum.—Nuttall, Fodor, Buchner, and others, have shown that lysins for various bacteria, such as the *V. cholerae*, *B. typhosus*, *B. coli*, and *B. dysenteriae*, are present in the serum of healthy individuals, as well as in that of infected or immunized ones. The quantity is, however, limited in amount. Thus, if a mixture of normal human serum with an equal volume of an emulsion of *B. typhosus* containing 10,000,000 organisms be incubated at 37° C. for one hour, the bacilli will all be destroyed, whereas after a similar procedure with an emulsion containing 20,000,000 per cubic centimetre, growth may be obtained on transferring some of the mixture to a suitable culture medium. By specific immunization of an animal a serum possessing vastly higher lytic power than this may be secured.

For certain bacteria, such as the *B. tuberculosis*, staphylococcus, and, according to Wright, the *B. pestis*, *M. melitensis*, *Streptococcus pyogenes*, and *B. diphtheriae*, there appears to be no lysin in normal human serum.

Quantitative Estimation of Lysin.—The evaluation of the lysin in a given sample of serum is a tedious process, and the result is not commensurate with the labour involved. The reason for this is that, as we have seen, two substances are concerned in lysis, and failure in its production may obviously be due to defect on the part of either. One of them, moreover—the complement—is held not to be present in the circulating blood, or only in very small quantity, so that estimation of the lytic value of the serum will give no indication of the actual value of the complement in the circulating blood. If, moreover, the complement be found in defect, we are faced by the fresh difficulty that we know at present of no means whereby this may be remedied. The statement that this can be done in animals by the injection of the sera of certain other animals has not been confirmed, while the attempt of Wassermann to excite the increased production of complement in guinea-pigs by inoculating them with anticomplements was not successful. That considerable fluctuations do occur in the amount of complement in the serum of human beings has been repeatedly demonstrated, but upon what this depends we know not at all. Increased formation of amboceptor can be easily stimulated, as has been mentioned, by therapeutic inoculation with graduated doses of a bacterial culture, dead or living, as the case may be.

Lytic Antisera.—As has been already mentioned, antisera, in some cases of exceedingly high lytic power, can be prepared in the case of those bacteria for which lysin in small amount is normally present in the serum by inoculating animals with graduated and carefully spaced cultures of the micro-organism. Shiga has determined the bacteriolytic power of his antidysenteric serum, and

found that 0.0001 c.c. sufficed to kill all the bacteria in $\frac{1}{500}$ milligramme of an agar culture. Assuming that *B. coli* and *B. dysenteriae* are of approximately equal weight, I have calculated that this is equivalent to saying that 1 c.c. of the serum would kill 160,000,000,000 *B. dysenteriae*.

The power of certain sera, such as that of antistreptococcic serum—an instance of a serum in the case of which we know not to what to attribute its protective and curative power—is estimated by determining the volume of serum which will just protect a small animal from a minimal lethal dose of bacteria, or from a certain multiple of that dose. Thus, 0.05 c.c. of antistreptococcic serum should suffice to preserve a rabbit from ten lethal doses of living streptococci injected intravenously. In the case of antityphoid serum, the usual method is to estimate its agglutinative power, and assume that this corresponds to its lytic power. The former may attain a strength which causes agglutination in a dilution of 1 in 1,000,000.

Experience with bacteriolytic sera has brought out one very interesting and very important fact—viz., that they protect against specific infection only when given in dosages within certain limits. Thus, Loeffler and Abel prepared an antiserum to the *B. coli*, and found that protection was afforded against a lethal dose of this organism only when a dose lying between the limits of 0.02 c.c. and 0.25 c.c. was given, and that larger as well as smaller doses were equally useless for the purpose. Similar results have been obtained with the other bacteriolytic sera, and throw some light upon the possible causes of failure experienced in the therapeutic application of certain lytic antisera.

The elaboration of lytic substances in man in response to preventive inoculation or to a living infection follows

the rules which apply to antibodies generally. Thus, inoculation with a small dose of dead typhoid bacilli results in an almost immediate response by the increased elaboration of lysin (as well as of agglutinin and opsonin). If the dose be increased beyond a certain magnitude, there may be produced a temporary lowering in the bactericidal power of the serum. This is followed within two to three days by a sudden rise, the maximum of production being attained in about seven days. Recent observations have shown that with such doses of typhoid vaccine as are commonly employed for immunizing purposes in man the period of diminished lytic power is of almost negligible duration. The curve of lysin so closely corresponds with that of agglutinin in these cases that the simpler determination of the latter is usually made, and the course of lysin production deduced therefrom.

In infective processes, also, the curves of lysin and agglutinin formation appear to correspond in a similar manner, and the points of prognostic importance already detailed for the one apply with equal truth, apparently, to the other.

4. OPSONINS.

In the case of the immune bodies already mentioned—viz., antitoxins, agglutinins, and lysins—it will be noticed that, although the elaboration of these bodies is attributed—at all events, in part—to the leucocytes, these latter play no subsequent part in the destruction of the bacilli or their products in virtue of the fact that these antibodies have exercised their prior actions—in other words, any effect which these antibodies and the leucocytes exercise upon the bacteria or their products is exercised independently of each other.

Quite otherwise is it with the antibody known as 'opsonin,' independently discovered by Wright and by Neufeld and Rimpau.

As each antibody has been discovered, to it in turn has been attributed the main rôle in the resistance of bacterial invasion, only for its importance to be discounted by the results of further study. The claims made on behalf of opsonins appear to rest on sounder foundations than those advanced in favour of the other antibodies. The result has been that the 'humoral' theory, which attributed protection to the destructive action of the serum on the microbes, has been discredited in favour of Metchnikoff's theory of phagocytosis, with this reservation, however—that whereas Metchnikoff believes that susceptibility to or immunity from infection is essentially a matter between the invading bacteria on the one hand and the leucocytes of the tissues on the other, the opsonic theory premises that before phagocytosis can occur the bacteria must undergo sensitization by opsonin, the leucocytes playing a more or less passive rôle in its absence. And whereas Metchnikoff would hold that the action of opsonin is a stimulating one upon the leucocytes, Wright has shown that opsonin has a specific affinity for the bacteria, and none for the leucocytes.

The Demonstration of Opsonin.—A little freshly-drawn blood is immediately received into eight or ten times its volume of 2 per cent. sodium citrate, to prevent coagulation. The blood cells are thrown down by rapidly centrifuging, and the supernatant liquid pipetted off. The cells are then thoroughly washed with a considerable bulk of a solution of 0.8 per cent. sodium chloride in distilled water, and again thrown down by means of the centrifuge, this process being repeated two or three times,

so that finally the cells are washed practically free from all blood-plasma, and are left suspended in a very small volume of the normal saline solution, as uniform a mixture as possible being made. A twelve to eighteen hour old culture on agar of any organism—say *Staphylococcus albus*—is then taken, and a thick emulsion made with a solution of 0·1 per cent. sodium chloride in distilled water. Clumps are thrown down by means of the centrifuge, and the bacterial emulsion divided into two parts, *A* and *B*. *A* is set aside ; to *B* an equal volume of fresh blood-serum is added, and the two thoroughly mixed together and heated in an incubator at 37° C. for fifteen minutes. The bacteria are thrown down by means of the centrifuge, and as much liquid as possible pipetted off. The precipitated bacteria are well washed with 0·1 per cent. solution of sodium chloride in distilled water, and again thrown down, this process being repeated several times. Finally, an emulsion of the bacteria is made in the salt solution exactly like *A*, and the numbers present respectively in emulsions *A* and *B* counted, the thicker emulsion being diluted to exactly the same strength as the weaker. We thus have a suspension of blood cells of which unit volumes contain the same number of polymorphonuclear white cells—*i.e.*, of phagocytes—and two emulsions of the same strength of a given organism in 0·1 per cent. salt solution, differing only in the fact that the bacteria in one (*B*) have been acted upon by blood-serum at 37° C. for fifteen minutes. If this has had no action upon the organisms, identical results should be obtained by the following procedure: Equal volumes of the blood cells and the bacterial emulsion *A* are thoroughly mixed together in a capillary pipette and incubated at 37° C. for fifteen minutes, the same being done with the substitution

of emulsion *B* for *A*. Films are spread, stained by Leishman's method, and observed under a $\frac{1}{12}$ -inch oil-immersion lens. The number of bacteria engorged by 100 polymorphonuclear leucocytes is then counted upon each film. An experiment performed in this way gave the following result :

Bacterial Emulsion employed.	Number of Cocci in 100 Polymorphonuclear Leucocytes.
<i>A</i>	10
<i>B</i>	500

It is thus obvious that some change is produced in the bacteria by the action of the blood-serum whereby phagocytosis is expedited. To the substance by which this change is brought about Wright gave the name 'opsonin.'

The combination of opsonin and bacteria has been found to go on, though more slowly, at ordinary temperatures and at 0° C.

Bacteria which have been acted on by opsonin may be heated to 60° C. for several hours without destruction of the opsonic effect of the serum, bacteria so treated being still readily taken up by well-washed leucocytes. There has thus occurred a stable union with the opsonin and a profound change in the bacteria, which are, however, unaltered in appearance, and are able to propagate themselves with apparently undiminished energy when placed in a suitable culture medium.

The Nature of Opsonins.—As opsonins have not yet been isolated in a pure state, the determination of their exact chemical nature has not been possible. They appear, however, to be non-dialyzable proteids of a colloidal nature related to euglobulin. Opsonins are highly but not absolutely specific bodies. That they are not absolutely specific is shown by the fact that the addition

of a very considerable amount of tubercle bacilli to serum will remove not only all the tuberculo-opsonin, but also almost all the staphylococcic opsonin as well.

That they are highly specific bodies is shown by many observations, such as the following :

1. A person suffering from a tuberculous infection may have an abnormal amount of opsonin for the tubercle bacillus, but normal amounts for all other bacteria.

2. After a therapeutic inoculation with, say, a dead culture of staphylococci, the amount of staphylococcic opsonin may be found to have been greatly altered, while the opsonin for other bacteria is quite unaffected.

3. In a person suffering from a double infection the opsonic curves for the two bacteria may follow quite independent courses.

The question whether opsonins are specific antibodies essentially different from all other known antibodies has been much debated, and not yet finally settled. One thing that has been proved is that the opsonins of normal and of immune sera are not identical. The opsonin of normal serum is thermolabile. Thus it is destroyed by heating to 55° C. for half to one hour. If kept at 60° C., most has disappeared at the end of five minutes, and but little is left at the end of fifteen minutes. This has suggested the view that the opsonins of normal sera are nothing but complement. Against this is the fact that complements are very slightly, if at all, specific, and it is very doubtful whether there are multiple complements present in the blood, and not only a single complement.

On the other hand, if the sera obtained from animals which have been highly immunized be heated, it is found that the opsonins are much more highly thermostable. Heating to 60° C. for fifteen minutes, as we have seen,

removes almost the whole of the opsonin from a normal serum, whereas it causes the disappearance of only a small portion of the opsonin from the immune sera.

Opsonic action, therefore, appears to depend on two substances—one thermolabile, the other thermostable. In normal serum the opsonin is almost entirely of the former variety ; in immune serum it is very largely of the latter variety. And just as it has been suggested that thermolabile opsonin is nothing but complement, so it has been suggested that thermostable opsonin is nothing but amboceptor. Wright, Hektoen, Neufeld, and others, are opposed to both these views, and maintain that opsonins are specific bodies, and form a class by themselves.

A discussion of the reasons for and against the various views would serve no useful purpose, and it may be stated as probable that opsonic action is the effect of two bodies acting together. The one, thermostable, is possibly amboceptor, and appears to have the power of sensitizing bacteria by itself : it is the essential substance ; the other, thermolabile, is possibly complement, and is capable of increasing the activity of the former body, or amboceptor.

The Source of Opsonins.—If thermolabile opsonin be identical with complement, its source must obviously be the same—*i.e.*, the polynuclear leucocytes. This is probably the case, although there has been shown to be no correspondence between the number of leucocytes in the blood and the amount of thermolabile opsonin. The fact, as shown by Eyre, that there is in pneumonia a rough agreement between the leucocytes and opsonin is beside the point, inasmuch as in a pneumonic attack the thermostable opsonin predominates over the thermolabile variety.

If thermostable opsonin be identical with amboceptor, its source should be the lymphoid tissues, bone-marrow, and spleen. These are in all probability the main, but not the only sources, for I have shown both in man and animals that if limbs be thoroughly perfused with normal salt solution to remove all blood, and the muscles cooled and mined, and their plasma extracted in the usual manner, its opsonic action, despite slight dilution with the saline solution used in the perfusion, is markedly higher than that of the blood-serum towards various organisms. In the instance of an amputated human leg, the index of the muscle plasma compared with that of the patient's serum was 1.4 towards the bacillus of Friedländer, the tubercle bacillus, and *Staphylococcus aureus*; in another case it was 1.3, from which it may be concluded that opsonin formation occurs in the muscle and subcutaneous tissues. The fact that injection into the subcutaneous or muscle tissue of small numbers of dead bacteria has a powerful effect in raising the opsonin in the serum points strongly in the same direction, for it is hardly likely that the injected bacteria ever reach the lymphoid tissues, spleen, or bone-marrow. The local elaboration of opsonin is, therefore, highly likely, and is probably performed by the lymphoid and endothelial cells.

Fate of Opsonins in the Organism.—As regards this point but little is known. It appears, however, that all exudates and secretions contain certain amounts of opsonin. Miller has found that it is contained in appreciable amount in the sweat, and to a larger degree in the urine, and that this excreted opsonin is increased during a negative phase consequent upon the injection of a bacterial vaccine. Milk also contains opsonin. The amount,

which is said to vary directly with that present in the blood, is said to be about one-fourth or one-fifth of that in the latter. It might, therefore, be concluded that the opsonin excreted in the mother's milk might be an important factor in the immunity of an infant to bacterial invasion.

Wells,¹ however, states, from a study of the opsonic indices of breast and artificially fed infants respectively, that in regard to opsonin the former enjoys no advantage over the latter.

THE RÔLE OF THE CELLS IN PHAGOCYTOSIS.

We have seen that leucocytes freed from all traces of serum, and suspended in normal salt solution, are practically unable to ingest bacteria or other foreign bodies unless these have first undergone the action of opsonin. The questions therefore arise whether the cells are nothing but passive agents, and whether there is no variation in the phagocytic power of cells of the same kind.

In disease processes we know that leucocytes are attracted to infected areas, but the actual ingestion of the bacteria appears to be there carried out without further active movement on the part of the leucocytes. Pseudopodia may perhaps be extruded, but there is no actual locomotive after the bacteria. The following experiment of Ponders shows the phenomenon of phagocytosis well: A drop of blood is put in a small glass cell, and a cover-slip placed over it. After incubation at 37° C. for fifteen to twenty minutes, the cover-slip is removed, and slip and cell washed with normal salt solution at 37° C. The red cells are thereby removed, and the leucocytes left

¹ *Practitioner*, May, 1908, p. 635.

adherent to the cell and cover-slip. The former is now filled with serum, a little bacterial emulsion added, the cover-slip replaced, and the cell kept at a temperature of 37° C. If a warm stage be employed, the process of phagocytosis may be observed under the microscope, and will be seen to proceed as follows : A bacillus lying within a certain distance of a leucocyte and in active Brownian movement is seen, despite oscillations in all directions, to be attracted to the leucocyte. This it approaches more and more nearly, until it comes in contact, and is finally ingested, perhaps by the extrusion of a pseudopodium.

Not all the cells of the blood are phagocytic. The polymorphonuclears and large lymphocytes certainly are, the small lymphocytes apparently not, and the eosinophyles certainly not. Of the other cells of the body, the epithelial and endothelial are actively phagocytic. The endothelial cells of the lungs and peritoncum, for instance, are among the most active in the whole body, and undergo a peculiar change in structure to fit them for the function. Ordinarily they are little more than thin plaques of protoplasm with a nucleus. When about to become phagocytic, they assume a columnar form, and are then often budded off as large round mononuclear cells, to which Metchnikoff has given the name of 'macrophages.'

The question as to whether all the cells of a given variety possess equal phagocytic powers is at once answered by the study of a stained film prepared from an incubated mixture of blood and bacteria. Some of the polynuclear cells will be crowded with bacteria, some will contain a few, and others none. There is thus a great difference in the phagocytic power of the cells of the same individual.

The question as to whether the average power of the

leucocytes of one individual is the same as that of those of another individual is usually answered, but incorrectly, in the affirmative. As a general rule, the correspondence is close in the case of healthy individuals, but sometimes there is a considerable divergence, especially in infected individuals. Bulloch and Ledingham have shown that the phagocytic power of the leucocytes set free from the bone-marrow in response to an injection of sodium einnamate is less than that of those in normal blood. Rosenow¹ has shown that the leucocytes from a case of pneumonia are, as a rule, hyperactively phagocytic.

Fleming states that their power is diminished, while Potter's observations reconcile these two divergent statements, as he found that the phagocytic power is at first above normal, but falls below it later, especially during convalescence.

Ledingham observed that the leucocytes of a case of myelogenous leukæmia were defective, and Bushnell the same in a leucocythæmic case.

Shattock and Dudgeon concluded that the cells vary in value like the serum in infected individuals, and Glynn and Cox² have found that this holds true in the case of healthy individuals as well as in the case of infected ones.

Bassett-Smith has shown that the leucocytes of a sufferer from Malta fever may appear to possess normal powers of phagocytosis when used in conjunction with a normal serum, but are decidedly more active when working in the patient's serum. Shattock and Dudgeon have confirmed this for other infections.

¹ *Journal of Infectious Diseases*, 1906, vol. iii., p. 683.

² *Journal of Pathology and Bacteriology*, 1909, vol. xiv., p. 90.

OBSERVATIONS ON THE PHAGOCYTTIC POWER OF THE BLOOD.

The first attempt at making an estimation of the phagocytic power of the blood was made by Leishman.¹ The procedure he devised was as follows: Equal volumes of blood drawn from the finger and of the bacterial emulsion were mixed together on a glass slide, and a cover-slip placed on top of the mixture, which was then put in an incubator at 37° C. for fifteen minutes. The edges of the cover-slip were then moistened with normal salt solution, and two films prepared by sliding the slip and slide apart. These were treated with the stain which Leishman devised for the purpose, and examined microscopically. The number of bacteria phagocytosed in a certain number of corpuscles were counted. The ratio of the former divided by the latter gave a measure of the phagocytic power of the given specimen of blood, and could be compared with the value simultaneously obtained with a specimen of normal blood.

The main objection to this technique is that the coagulation of the blood which speedily occurs interferes both with the process of phagocytosis and with the preparation and examination of the films. Various modifications have therefore been introduced, and while the method of Wright and Douglas is the most important one, it is more convenient next to consider the method known as that for the determination of the *haemophagocytic index*, as more closely resembling the original. Here the coagulation of the blood is prevented by the decalcifying action of sodium citrate, and the incubation of the mixed blood

¹ *British Medical Journal*, January 11, 1902.

and bacteria is conducted in capillary tubes, as devised by Wright. The method itself he abandoned in favour of that for the opsonic index, but it was subsequently revived by Stewart, Dodds, and Veitch. Of each blood that is to be examined, and of a blood which is considered to be normal and is to serve as the 'control,' a unit volume is taken and at once mixed thoroughly with an equal volume of an aqueous solution containing 0·8 per cent. sodium chloride and 2 per cent. sodium citrate. The phagocytic mixtures are made by taking 2 volumes of each of these citrated bloods and 1 volume of the bacterial emulsion. These are mixed thoroughly together on a glass slide, and the mixture drawn by means of a teat into a fine capillary tube, so that it lies somewhere about the middle of the capillary tube. The free end of the latter is then sealed in the Buusen flame, and when the various mixtures have been completed the tubes are all placed in an incubator at 37° C. for fifteen minutes, after which the contents of each tube are expelled on to a clean glass slide, remixed by aspirating and blowing out several times, and finally two films are prepared from each specimen. The technique of the whole procedure will be better understood when Wright's method has been explained. The films are stained with Leishman's stain and examined microscopically, and the number of bacteria phagocytosed by, say, 100 consecutive polymorphonuclear cells in each specimen are counted. The ratio of the numbers found for the 'test' bloods divided by the number found for the 'control' blood—the contents of the same number of corpuscles being counted in each—yields the '*hæmophagocytic index*.'

The advantages of this method are that it is free from complications, speedy, and easy of performance. It also

gives an accurate comparative estimation of the total phagocytic power of the blood in question, any variation in the phagocytic power of the polymorphonuclear cells being jointly determined with any variation in the content in opsonin of the plasma. It also possesses this merit—the blood is altered as little as possible, and is not subjected to coagulation, which may materially affect the nature and amount of the immune bodies present.

The chief objection which has been taken to this method is that the joint estimation of the opsonin content of the plasma and of the phagocytic activity of the individual's cells gives a result which is the resultant of two different factors, which may both be variable, and that, accordingly, we learn nothing about each individual factor. This is perfectly true; but on the one hand there is the fact that the phagocytic power of the corpuscles of most individuals varies but little from the normal even in disease, and when such a variation does occur, it is surely unwise to disregard it; and on the other hand there is the objection that the alternative procedure of Wright, who holds the above objection most strongly, not only takes no cognizance of the possible variation in the phagocytes, but does not even evaluate the opsonin content of the plasma, but of an artifact, the serum. No satisfactory proof is yet forthcoming that the two are identical or even necessarily comparable, though it is highly probable that as a rule they are approximately equal.

WRIGHT AND DOUGLAS'S METHOD OF DETERMINING THE
OPSONIC CONTENT OF THE SERUM.

This is a frank attempt to make a comparative estimate of one only of the constituents of the blood upon which phagocytosis depends. Inasmuch, however, as upon the lessons learnt from this procedure has the whole fabric of vaccine treatment been built, it is necessary to describe it in some detail. The principle of the method is described by Wright in the following words: 'An aliquot part of the patient's serum, measured in a capillary pipette, is mixed with an equal volume of a bacterial suspension and a like volume of a suspension of washed leucocytes derived from a normal blood. After this phagocytic mixture has been digested for a suitable period at 37° C., film preparations are made and stained. A phagocytic count is then undertaken—i.e., the average bacterial ingest of the leucocytes in the phagocytic mixture is determined, and this is compared with the average ingest of the leucocytes in a phagocytic mixture made with normal blood. The expression thus obtained—

Average ingest of the individual phagocyte in the mixture
containing the patient's serum

Average ingest of the individual phagocyte in the mixture
containing the normal serum

—is denoted the opsonic index.

'In order that the procedure shall yield a satisfactory measure, many precautions in technique are necessary, and it is essential also—(1) that proper controls should be employed; (2) that a reasonable amount of phagocytosis should be obtained in the control serum; (3) that spontaneous phagocytosis should be suppressed; (4) that the ingest of a sufficiently large number of phagocytes should be counted.'

As briefly as possible I propose to describe how the various essentials to success may be secured, and how the introduction of various fallacies may be obviated.

The constituent elements of the test are as follows :

1. Sera : Control and of the various patients whose bloods are to be investigated.

2. Phagocytic cells.

3. A suspension of the bacteria against which the opsonic contents of the several bloods are to be determined.

Let us consider these individually :

1. *Control Serum*.—Inasmuch as slight variations have been found in the opsonic content of the blood from different individuals apparently free from bacterial infection, it is considered advisable to employ as the standard serum, not the serum derived from any one apparently normal individual, but a mixture of the sera derived from several such individuals. This 'pooled' serum is held to furnish an unvarying standard for reference. It will therefore be understood that when the control serum is mentioned, such a 'pooled' serum is intended.

In the collection of the various sera, control and otherwise, certain precautions are necessary :

- (1) The blood should flow freely and without need of the application of pressure or massage from a puncture, best made with a sterile surgical needle, either on the lobe of the ear or the finger-tip. The site of election should be first cleansed with alcohol, then with ether, and allowed to dry.

- (2) The freely-flowing blood is to be received in a sterile receptacle, which may be either a Wright's collecting-tube or a straight piece of glass tubing of an external diameter of about $\frac{3}{16}$ inch, and of a length of about 3 inches. The

ends having been drawn out into capillary threads, which have been then cut off short, these are to be held horizontal to the ground, and the blood allowed to run in by capillary attraction until they are about half full. The blood must not be allowed to reach the end remote from the patient.

(3) Inasmuch as heating to over 60° C. injures opsonin, heating of the contained blood must be carefully avoided. The sealing of the tubes is best done as follows : The tube is carefully maintained in a horizontal position, about $\frac{1}{4}$ inch of the end remote from the blood is very gently warmed in the tip of the spirit-lamp or Bunsen flame, and the capillary end sealed in the flame. The tube is then laid down and allowed to cool. The contraction of the warm air in the sealed end of the tube withdraws the blood slowly out of the capillary end which was used for the collection of the blood, and allows the sealing of this end to be performed without any risk of heating the contained blood. When the tube has again cooled down completely, the contained blood should be shaken down into one extremity of the tube, and coagulation allowed to proceed.

(4) Although the opsonin of the serum shows very little diminution in amount, even after twenty-four hours at room temperature, it is always well to collect the control bloods at the same time as the patient's, or, if this cannot be done, to place them in an ice-chest as soon after collection as possible.

(5) When coagulation has been completed, it is necessary to be able to remove the serum free from admixture with blood cells. The tubes should therefore be centrifugalized until a clear layer of serum is seen above the blood-clot, and the pipetting off of the serum must be so

performed as not to cause the liberation of blood cells from the clot.

(6) Very occasionally after coagulation has occurred it will be noticed that the serum is tinted red. In such cases the most likely cause of this is overheating of the blood during sealing of the tubes; but should this have been avoided, it is possible that the blood contains an iso-hæmolysin—*i.e.*, a lysin for its own red blood cells. In either case a reliable measure of the opsonic content cannot be obtained.

2. *The Phagocytic Cells.*—These are to consist of the polymorphonuclear leucocytes of a healthy individual free from any admixture with serum. As usually obtained, the leucocytes are admixed with red blood cells. Inasmuch, therefore, as the red blood cells of certain individuals are apt to agglutinate with the sera of others, and any agglutination occurring in the phagocytic mixture results in a lowering of the opsonic effect, it is necessary to collect the blood which is to be used for the preparation of the phagocytic cells from a person whose corpuscles have been ascertained to be insensitive to agglutinative action.

The procedure is as follows: 4 c.c. of a sterile freshly-prepared 2 per cent. solution of sodium citrate in distilled water is placed in a sterile 10 c.c. centrifuge tube; the finger-tip of the selected individual is sterilized, sharply punctured, and 1 c.c. of the blood allowed to flow into the citrate solution, which is well agitated to insure due mixture. The tube is then placed in an efficient centrifuge, counterpoised carefully, and centrifugalized steadily at a high speed till all the corpuscles appear to have been thrown down. This will have occurred when the deposited blood cells occupy a volume of about $\frac{3}{4}$ c.c. As

the white cells are lighter than the red, they tend to be thrown down last. If too low a speed of the centrifuge be employed, they may form a dense layer on top of the red cells, and their subsequent separation from each other may present difficulties. As the occurrence of clumped phagocytes in the phagocytic mixture will give an erroneous evaluation of the opsonin, this must be avoided. The maintenance of a sufficiently high speed of the centrifuge will effect this, and cause their more uniform deposition among the red cells. When the desired result has been secured, the supernatant clear fluid, citrate solution, and plasma, is pipetted off as completely as possible without disturbance of the deposited corpuscles. The centrifuge tube is then filled up to the 5 c.c. mark with sterile 1 per cent. salt solution, the corpuscles well dispersed throughout the fluid, and the mixture centrifugalized as before. The clear fluid is again pipetted off, and the washing process twice repeated. Finally, the deposited cells are suspended as uniformly as possible in sterile 1 per cent. salt solution, this latter being added till the total volume, cells and salt solution, equals that of blood originally taken—*i.e.*, 1 c.c.

The suspension of the corpuscles is made in 1 per cent. instead of in 0.8 per cent. salt solution, because Douglas has shown that spontaneous phagocytosis of the bacilli is thereby reduced to a minimum.

Such a suspension, when examined under the microscope, should show the polymorphonuclear leucocytes uniformly distributed among the red cells, and not aggregated into clumps.

When mixed with small quantities of the sera to be tested, no agglutination of the red blood cells of the mixture should be perceptible.

Russ¹ has devised a method for obtaining the leucocytes for the phagocytic mixture free from red blood cells, whereby he claims that counting of the slides is greatly facilitated, and experimental error considerably reduced.

The procedure depends on an observation by Ponder, and is as follows : A rubber ring placed on a clean glass plate is filled with blood, and covered by a second similar plate. Incubation at 37.4° C. is conducted for twenty minutes. The covering plate is then removed, the ring and clot lifted away, and the plates washed with 1.25 per cent. salt solution, to free them from red cells and serum. After wiping the ring margin clear of more red cells and dried serum, a few drops of cold 1.25 per cent. salt solution are poured on the leucocyte-laden area of each plate. These are then replaced in the incubator for fifteen minutes. This causes the polymorphonuclear cells to resume their proper shape—they are previously somewhat distorted—and to free themselves from the plate. By means of a glass rod the fluid and floating leucocytes are swept into a small tube, and concentrated by the centrifuge at a moderate speed. Some of the supernatant liquid is pipetted off, the white cells being then distributed by agitation with the remaining fluid. Experiment has not yet determined whether such leucocytes are entirely suitable for comparative opsonic estimations. From Russ's observations it would appear that this is the case.

3. *The Bacterial Suspension* must fulfil the following conditions :

(1) It must be perfectly uniform, free from clumps, and must not undergo agglutination, either spontaneous or with the sera to be tested.

¹ Proceedings of the Royal Society of Medicine, 1912, vol. v. No. 7, p. 187, Pathological Section.

(2) It must consist of elements which stain evenly and well.

(3) Its use must be free from serious danger.

(4) It must be of such a strength as to give a leucocytic ingest which will enable adequate differentiation to be made of the opsonin content of the various sera should differences exist.

Let us consider each of these points seriatim :

(1) It is a comparatively easy matter to secure a uniform emulsion of many bacteria, especially of the motile ones, such as *B. coli* and *B. typhosus*. Staphylococci, streptococci, and pneumococci, are others which, as a rule, present no difficulties. Two or three drops of 1 per cent. salt solution are placed on a watch-glass, and one or two loopfuls of the bacterial growth are carefully mixed with these by means of a glass rod. Fresh salt solution is then added, and the mixture completed. The emulsion is now pipetted into the hæmatocrite tubes of the centrifuge, and centrifugalization maintained at a high speed for three to four minutes. The upper portions are then carefully pipetted off, diluted if desired, and well mixed by means of the pipette.

With other bacteria, such as the tubercle bacillus and *M. catarrhalis*, considerable difficulty may be encountered. They may prove to be very difficult of separation into their component elements in the first place, and, when separated, may agglutinate spontaneously in the second. In the majority of such instances it is found that heating of the bacterial growth for a few minutes to 100° C., or just below this temperature, will obviate both these difficulties. The emulsification and subsequent centrifugalization must be very thoroughly performed, and 1 per cent. salt solution used as the suspending medium.

(2) In order that the phagocytosed bacteria should stain clearly and deeply, it is necessary that young cultures should be used. An eighteen-hour culture of the freely-growing organisms and a seven days' growth of tubercle bacilli yield satisfactory results. This point is of especial importance when we are dealing with such organisms as the typhoid bacillus, for which lysin may be present in the sera. Here we may be also compelled to destroy the lysin, agglutinin, and non-specific opsonin, by heating the sera to 58° C. for fifteen to twenty minutes prior to making the phagocytic mixture. In certain instances, such as those of the glanders bacillus and Bordet's bacillus, adequate staining of the bacteria in a phagocytic mixture is almost impossible of attainment. Rather restricted decolorization of the Leishman stain or subsequent counter-staining with 1 per cent. toluedene blue will help to get over this difficulty.

(3) An emulsion which fails to yield a count of at least 250 bacilli within 100 leucocytes in the finished film is too weak to yield a satisfactory differential count. A count of 500 bacilli in 100 leucocytes of the 'control' film is highly desirable. Experience will aid greatly in estimating the requisite opacity of the bacterial suspensions, while a preliminary test with the leucocytes and a normal serum, as Wright suggests, will afford even better indication as to whether the emulsion is too weak or requires dilution. As a general rule, a suspension containing 500,000,000 bacilli in each cubic centimetre will prove satisfactory. In the case of some bacteria, such as the meningococcus and some virulent strains of the pneumococcus, normal sera may produce little or no opsonic effect, so that it is impossible to secure any reliable 'control' count. The sera of infected individuals may,

on the contrary, be capable of producing marked opsonization, so that very high opsonic indices may be obtained. The only way out of this difficulty is to employ strains of these bacteria which have been repeatedly subcultured or derived from another source, and proved to be capable of opsonization by a normal serum.

(4) In order to obviate the danger to the operator attending work with such highly dangerous bacilli as the glanders or tubercle bacillus, it is well to employ killed cultures of these bacteria for opsonic work. Little or no error appears to be introduced by this measure.

Furnished with the 'control' and 'test' sera, with a satisfactory suspension of leucocytes and emulsion of bacteria, we are in a position to proceed with the test. The materials required are—(1) Incubator maintained at 37° C. (2) Clean glass slides, one side of which has been slightly roughened by rubbing with very fine emery-paper, such as watchmakers use. (3) A supply of spreaders made either by cutting some of the slides down the centre longitudinally with a diamond and completing the fracture, or by snapping some of them across their short diameters and cutting off the corners of the fractured edges with a diamond. As satisfactory spreaders are an important essential, it is wise to test their capacity for giving a satisfactory film beforehand, and cleanse thoroughly those which fulfil our requirements. (4) Appropriate fixing and staining solutions. For all bacteria, except the tubercle and leprosy bacillus, Leishman's stain is well adapted for both fixation and staining purposes. Films containing the tubercle bacillus require fixing either with formaldehyde vapour or methyl alcohol prior to staining with warm carbol fuchsin. Five per cent. sulphuric or nitric acid serves for decolorizing purposes, and a 1 per cent.

aqueous solution of toluidene blue as an admirable counter-stain. (5) Porcelain jars with metal covers for holding slides during fixation and staining. The carbol-fuchsin contents of these can be maintained at a suitable temperature for staining purposes by placing the jars in the incubator, and the vertical position in which the slides are held prevents the deposition of particles from the stain upon the films. (6) A supply of capillary pipettes of approximately the same fine bore. These are made by taking 6-inch lengths of clean glass tubing of $\frac{5}{16}$ inch external diameter, heating them in the middle in the tip of the blow-pipe or Bunsen flame till about a $\frac{1}{2}$ -inch length of the tubing is quite soft, removing them from the flame, and, by rapidly separating the two hands, drawing out the molten glass to a length of 18 to 20 inches. By means of a fine file the capillary threads are cut across, so that a length of 6 to 8 inches is left attached to each piece of tubing. The end of each of the latter is then lightly plugged with cotton-wool and a strong rubber teat applied. By means of a grease pencil a fine mark is made about $\frac{3}{4}$ inch from the free end of each capillary thread, to indicate the unit volume.

The procedure is now as follows: By means of a capillary pipette and rubber teat the unit volume of blood cells, as indicated by the pencil mark, is taken up into the capillary thread. A tiny bubble of air is now allowed to enter the thread, and then one volume of the bacterial emulsion taken up as before; now another air-bubble, and finally one volume of serum, so that we have in order in the capillary tube from above downwards one volume of blood cells, air-bubble, one volume of bacterial emulsion, air-bubble, one volume of serum. It is highly important that this precise order should always be

maintained. By making gentle pressure on the teat, these are then all blown out on the surface of a clean glass slide and perfect mixture made by alternate aspiration into and expulsion from the capillary tube. When this has been completed, the whole is carefully reaspirated into the capillary thread, so that the mixture occupies the region about its middle. Carefully maintaining an even pressure on the teat, the tip of the thread is sealed by its momentary introduction into the Bunsen flame. The rubber teat is removed, and by means of the grease pencil the tube is marked with the name or number of the serum, and laid aside on the bench till the various phagocytic mixtures have been completed. The phagocytosis which proceeds during this varying period of delay is very slight at the temperature of the room, but it is none the less wise to make two control mixtures—one at the beginning, the other at the end of the whole procedure—and to mark them accordingly. Any appreciable difference in the counts of the two will indicate an unreliable result, and the necessity for repetition. If many sera have to be examined, it is perhaps well to divide them into batches of six to eight, controls being done for each batch. The phagocytic mixtures are then placed in the incubator at 37° C., as a rule for fifteen minutes, but in the case of such bacteria as *B. typhosus* and *B. coli*, for which lysin and agglutinin are present in most sera, the period may be advantageously reduced to one of ten minutes.

The tubes are then removed from the incubator, the capillary teats readjusted, the tip of the threads scratched with a file and broken cleanly off. The phagocytic mixture is expelled on a clean glass slide, and perfect mixture made as before. The whole is then reaspirated into the capillary tube, and a small drop of the mixture

carefully placed on the roughened surface of each of two of our clean slides about $\frac{3}{4}$ inch from one extremity. The spreader is then applied to the drop, held at an angle of about 45 degrees to the vertical, and with the application of moderate pressure the drop of mixture is distributed uniformly along about $1\frac{1}{2}$ inches of the surface of the slide. The preparations are made in duplicate for this reason: one smear is sometimes more perfect than the other, but may be spoilt in staining. We then have the second to fall back on, and are not put to the necessity of repeating the whole procedure, not only with the serum in question, but also necessarily with the control.

Each slide is then marked with the corresponding name or number, and set aside to dry in the air.

When the preparations have been completed, it remains to stain the smears appropriately and make the phagocytic counts.

The method adapted to the former end will depend upon the organism with which we are working. If it be the tubercle or lepra bacillus, it will be necessary to stain the bacteria first and the phagocytic cells afterwards. This is done as follows: Into the porcelain staining-jar two or three drops of formalin or a quantity of methyl alcohol sufficient to cover the slides is placed, the slides inserted vertically into the grooves in the jar, and the metal cover put on. After one to two minutes fixation is complete, the slides are removed, lightly blotted if methyl alcohol be the fixation employed, and allowed to dry in the air. A similar staining-jar is then nearly filled with hot carbol fuchsin, the slides inserted as before, cover replaced, and jar put in the incubator for ten to fifteen minutes, when the slides are removed, washed under the tap, drained, and the 5 per cent. solution of

nitric or sulphuric acid poured over the films, and allowed to remain on for half a minute. It is then washed off thoroughly under the tap. A 4 per cent. aqueous solution of acetic acid is applied, to remove the hæmoglobin from the red cells and expedite subsequent examination. This is quickly washed off as before, the films lightly blotted, and the 1 per cent. aqueous solution of toluidene blue applied for sixty to ninety seconds. This is removed by thorough washing under the tap, the films lightly blotted, and dried by gentle heating. The tubercle bacilli will be stained red by the carbol fuchsin, the phagocytes blue by the toluidene blue.

For most other bacteria Leishman's stain affords not only adequate fixation, but also good differential staining of the bacteria and phagocytes. The slides are placed film upwards, and covered with the stain. After one and a half to two minutes the slides are flooded with distilled water, which is well mixed with the stain, and allowed to remain on for five to ten minutes. It is then drained off, and the films washed in a dish containing plenty of distilled water until, on removing them from the dish, no further tinting of the adherent drops of water with blue is observed. They are then lightly blotted and quickly dried. The bacilli are stained deep blue, the cell nuclei blue, and the cytoplasm reddish.

If such a phagocytic film be observed under the $\frac{1}{12}$ -inch objective of the microscope, the polymorphonuclear cells will be seen not to be uniformly distributed throughout the film, but to be collected towards the edges and the end at which the spreading was completed. The individual leucocytes should not, however, be aggregated together, but be separate from each other.

It now remains to estimate the phagocytic ingest. For

this purpose the $\frac{1}{2}$ -inch objective of a microscope with mechanical stage is requisite, while counting is facilitated by drawing with a well-sharpened grease pencil two fine diameters at right angles to each other on the eye-piece. The edge of the film is now examined, and the number of bacteria found in each series of five consecutive phagocytes noted. If the technique throughout has been satisfactory, no great divergence should be found in the count yielded by each consecutive set of five cells. If the films be thoroughly satisfactory ones, the time and labour involved in estimating the ingest of 100 leucocytes is not considerable; but if there be a deficiency of white cells, this is correspondingly increased. No arbitrary limit can be fixed as to the number of phagocytes which must be observed in order to obtain a reliable result. If the correspondence between the ingest of each set of five cells is close, 100 cells may more than suffice; if it be not close, this number may need increasing considerably—say, to even 250 cells. If the divergence be due to the fact that every now and again one cell has a considerably higher ingest than others, a decision will have to be made as to whether a hyperactivity of the cell or an error of technique is to be held responsible. If the bacteria are all separate, the former deduction may be safely made, and the experiment will stand good. If the bacteria are all clumped together, lack of care in preparing the bacterial emulsion or the presence of agglutinin in the serum must be assumed, and the experiment must be repeated with fresh precautions.

When the phagocytic count of each preparation has been completed, the index is determined as follows: If the same number of cells has been observed in each, the number of bacteria counted in each patient's film is

divided by the mean between the numbers found in the two control films. Suppose, for example, that in patient A's film 100 phagocytes contain 300 bacteria, and 100 phagocytes in the one control contain 480 and in the other 520 bacteria, the opsonic index of the patient's serum is given by dividing 300 by the mean between 480 and 520—*i.e.*, by 500—that is, the index is 0.6. If different numbers of cells have been observed, then the number of bacteria counted in each slide is divided by the number of cells observed, this giving the phagocytic index. The opsonic index is then given by the ratio—

$$\frac{\text{Patient's phagocytic index}}{\text{Control's phagocytic index}}$$

Objections to this Method of determining the Index.

The question has been much debated as to the degree of accuracy with which the estimation of the opsonic index can be made. No useful purpose would be served by once more entering the arena. I am bigoted enough to maintain still my well-known views upon this matter. Accurate results are obtainable by one only who is skilled in the technique of laboratory work generally, and in the technique of this intricate procedure in particular. There are pitfalls innumerable to be avoided, and experience will alone teach how this is to be done. No one is foolish enough to claim mathematical accuracy for the method, but in skilled hands the error should practically never exceed 10 per cent., and should the more often only be about half this amount. This is the mature opinion I arrived at only after the performance of many hundred control experiments, and it is also the opinion of those who have had any long experience of the method. In

unskilled hands the error may be of any magnitude. None the less, the hostile criticism has not been devoid of good. It has led to a closer scrutiny for possible sources of error, and the obviation of these by improvements in technique.

Objections based on other considerations than those of mathematical accuracy have been advanced against the determination of the opsonic index. Some of these have been already hinted at. These may be considered in more detail along with others.

In the first place, the method, frankly, is merely an attempt to estimate one of the factors concerned in phagocytosis—viz., the opsonin content of the serum. Wright maintains that there is a greater utility in determining one only of the variable factors than in determining the influence of at least two variable factors summed together, as is done in the case of the hæmophagocytic index. This is a matter of opinion, and may be true in some cases, but not in others. That the intrinsic activity of the phagocytes may vary greatly must be assumed as demonstrated, and personally I feel that it is best to learn what is the total comparative defensive phagocytic power of the individual rather than what is the comparative value of one of the factors contained in a fluid which is not present as such in the body. The opsonin content of plasma and of serum derived from that plasma is not necessarily the same.

A further objection may be urged to the estimation of the hæmophagocytic and opsonic index alike—an objection which holds with particular force so far as the tubercle bacillus is concerned—that for the evaluation the phagocytic energies of the polymorphonuclear leucocytes are

employed; that prior opsonization of the bacilli is necessary for active phagocytosis by the polymorphonuclear cells is beyond dispute, but no demonstration has yet been offered that this also holds for the lymphoid and endothelial cells. Inasmuch as these latter cells are held to be the source of the opsonin in the body, the reverse assumption might with some justice be advanced. Now, phagocytosis of the tubercle bacillus is normally performed, not by the polymorphonuclear leucocytes which require prior opsonization of the bacilli, but by the lymphoid and endothelial cells, which may well be capable of dispensing with this preliminary. It might well be asked, therefore, what earthly use is there in determining the phagocytosis performed by certain cells which normally do not perform the task after opsonization of the bacilli when normally this may not be requisite? These are weighty objections, but their weight is minimized by the results of experience, by the correlation of estimations of the opsonic index with clinical observations, whereby we learn that whatever may be the deficiencies of the method, it yet does furnish something of a reliable guide to the processes whereby the body tissues defend themselves against invasion by the tubercle bacillus.

A further objection to the rationale of the method has been taken by Klein, Neufeld, Simon, Walker, Lamar, and others. It is based upon the fact that, unless bacterial emulsions of a strength far greater than is usually employed are utilized, more than sufficient opsonin is present in all sera for the complete opsonization of the bacteria.

OTHER METHODS OF ESTIMATING OPSONIN IN THE SERUM.

Simon and Walker therefore consider that, inasmuch as the use of very thick emulsions has obvious disadvantages, the best procedure is to dilute the sera ten to thirty times, and after incubating with a bacterial emulsion of considerable strength, to compare the percentage of phagocytizing leucocytes in the specimens of blood to be investigated with the figure obtained after a similar procedure with a specimen of normal blood. This they call the 'percentage index,' and find that it sometimes yields results agreeing well with the opsonic index, but sometimes differing widely from it. In order to carry out this method successfully, it is necessary to standardize the bacterial emulsion, so that the mixture with the control diluted serum may yield a proportion of cells which have not performed phagocytosis. The great objection, to my mind, in this procedure is that, while in Wright's method a number of bacteria are offered to the leucocytes for phagocytosis altogether out of proportion to what ever exists either in the blood or locally in an infected focus, in this method that utterly abnormal condition is further accentuated. At the same time, it must be admitted that this 'dilution method' at times affords a more accurate idea of the total amount of opsonin present in the serum.

In the methods of Klein and Neufeld the procedure is carried even farther. They dispense with the use of a control blood, and make a series of phagocytic mixtures with progressive dilution of the serum in normal salt solution, and count the ingest of the phagocytes in the whole series of preparations until they ascertain the

dilution in which the phagocytic count is identical with that obtained in a mixture in which plain normal salt solution is used without any serum. This is known as the 'method of extinction,' is extremely laborious, and, in addition, suffers from the same objection as the 'dilution method.'

CHAPTER II

THE VALUE OF OPSONIC INDEX ESTIMATIONS IN DIAGNOSIS, PROGNOSIS, AND TREATMENT

It little matters what objections may be urged theoretically against the various procedures for estimating the opsonin content of the serum or the hæmophagocytic power of the blood if the practical advantages derived from their application are real ones and commensurate with the time and labour involved. As we have already discussed the theoretical objections, it now behoves us to learn what practical lessons and advantages are to be derived from such investigations. To this end it is necessary to ascertain if any variations are to be detected in the blood of diseased individuals as compared with that of healthy ones ; if such variations do exist, to learn their import ; the bearing that they have on the clinical condition of the patient, and how they are to be controlled and influenced to his advantage. Inasmuch as by far the most thorough investigations upon these points have been conducted by means of opsonic index estimations, it is obviously best to devote our attention to this particular method.

THE OPSONIC INDEX IN HEALTH.

Firstly, we must consider whether the opsonic indices of all ' normal ' individuals are the same, or whether they

exhibit variations, and, if so, to what factors are these variations to be attributed.

We have seen that, in addition to the errors inherent in the method, numerous sources of error may be introduced into the evaluation of the opsonic index by Wright's method; that how great these will be depends on the skill, technique, and experience of the worker; and that in thoroughly competent hands the margin of error should not exceed 10 per cent.

If we allow a margin of error of 10 per cent. in either direction, and assume that the blood of all normal individuals contains precisely the same amount of opsonin, it follows that the index of any normal individual, as estimated by the method, should be found to lie between the limits 0·9 and 1·1. Many thousands of such observations have now been made, with the result that the limits have been found of wider range than this—viz., 0·8 to 1·2. Such a variation of 50 per cent. lies quite outside that which can possibly be attributed to experimental error.

When we talk of 'normal' individuals in this connection we mean such individuals as are at the time clinically free from all infection by the bacterium in question. For instance, it is highly probable that all at some time or another have been infected by the *B. tuberculosis*. A 'normal' individual in connection with this organism can therefore only be one in whom all clinical and other evidence justifies the view that complete recovery from the infection was made at some distant date. The fact that the widest variations in the opsonic index of 'normal' individuals are found in regard to the index towards the *B. tuberculosis* is indicative of this almost universal infection, and the persistence of small amounts of the corresponding 'immune bodies.'

The necessity of employing the pooled sera of several 'normal' individuals as the 'control' serum, more especially in determinations of opsonic indices towards the *B. tuberculosis*, is therefore evident, and the advisability of not attaching too much importance to values even a little outside the above 'normal' limit 0·8 to 1·2, especially if the values obtained for any given individual remain constant from time to time, is equally obvious. In the case of other such omnipresent organisms, as the *B. coli* and staphylococcus, it is also difficult to see how any individual can have altogether escaped active infection at some period of his life. In other words, the strictly 'normal' individual can hardly have existence. Nevertheless, in those who at the time of investigation appear to be clinically free from all such infection, values for the opsonic indices very closely approximating to unity are uniformly obtained. The index of the average healthy individual towards the staphylococcus has been found to lie between 0·9 and 1·1.

We may therefore generalize, and say that the opsonic index of the clinically healthy individual to *all* pathogenic organisms should lie between the limits 0·8 and 1·2, and to most between 0·9 and 1·1. Urwick has observed the tubercle opsonic index of healthy individuals from day to day, French the effect of hard exercise, Charteris the effect of fasting, and I myself the combined effect of fasting and exercise. All agree in finding variations, but such variations as lie within the normal limits, and almost the limits of experimental error alone.

There are, however, two factors which appear to cause wider fluctuations in the index—namely, menstruations and age. The near approach of menstruation appears to cause a general depression of the index to all organisms,

which the initiation of the flow appears to correct, the normal index being re-established by the second or third day.

Wells and Frecman studied the opsonic indices of infants from birth up to one year of age. They found that the index was normal at birth, but later was subject to very great fluctuations. They concluded—(1) that a low index is not diagnostic in children under one year of age ; (2) that a low opsonic index in infants is not inconsistent with health, and that a child may be thriving well with a declining index ; (3) that their antibacterial defence cannot depend upon the opsonic content of the serum.

THE OPSONIC INDEX IN DISEASE.

Having thus made the assumption that variations in the opsonic index between the limits of 0·8 and 1·2 are not inconsistent with a clinical condition of perfect health, it becomes necessary to make study of the indices found in the various pathological bacterial conditions, and ascertain if these diverge from the normal limits, and, if so, to elucidate how these divergencies are brought about, how they are to be interpreted as bearing on the clinical condition of the patient, and how they may be utilized in diagnosis and in treatment.

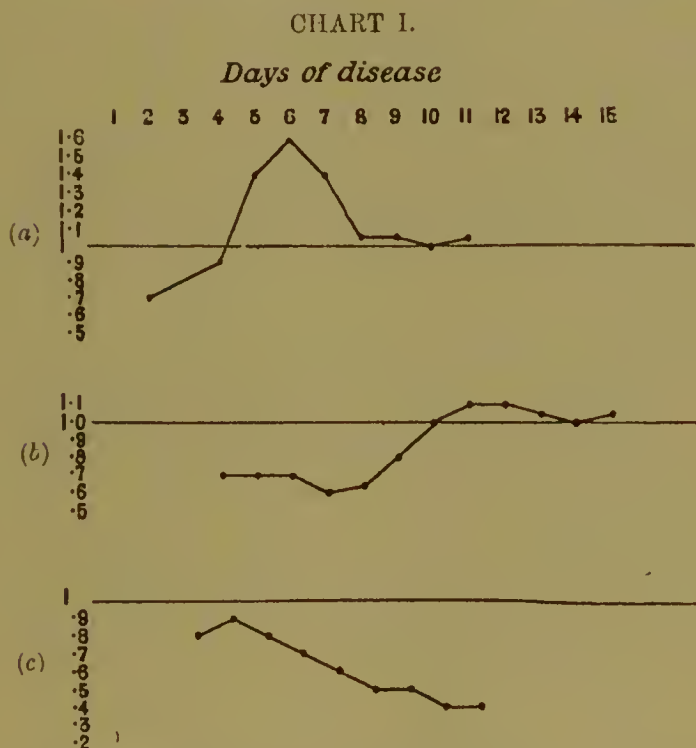
The results of many thousand observations of the opsonic index in cases of bacterial infection have conclusively demonstrated the existence, at some period or another of the attack, of a considerable divergence from the normal range of index, and that the nature of these divergencies depends largely upon the nature of the infection. For instance, if a series of observations be made from day to day in a case of a chronic infection by the

staphylococcus, such as acne, which shows no tendency to spontaneous recovery, they will reveal the fact that the opsonic index as a rule maintains a level constantly below the normal, varying, perhaps, between the limits 0.4 and 0.8. If, on the other hand, a similar study be made in the case of an acute infection by that organism, such as that of a solitary boil, it will be found that the curve of the opsonic index follows a more or less definite course from day to day. At the onset of infection the index may, for example, be 0.7; as the lesion makes headway the index may fall steadily from 0.7 to 0.4, and remain for some time at this lowest level, this period corresponding to that at which the infection is at its worst. When recovery begins, the index will be found to rise, and rise, perhaps, with a much greater rapidity than that with which it fell, so that at the completion of recovery it may reach a level of 1.4 or over. If the boil be a solitary one, a slow and gradual decline of the index will set in shortly, until, after a very variable period, it will be found to have assumed a steady position within the normal limits; but should a fresh boil make appearance a few days after the healing of the first, the index curve will be found to have made a sudden drop from the high level more or less coincident with the appearance of the second lesion, recovery to a high level being once more made as healing again takes place.

The curve of the opsonic index has been carefully studied for most acute bacterial diseases, and it has been found that in cases which pursue a normal course to recovery, as a rule the index is low at the inception of the attack, falls, perhaps, still lower as the disease makes headway, remains at this low level during the height of the attack, and rises suddenly or gradually when defer-

vescence occurs, the sudden rise occurring when recovery is quick, the more gradual rise when recovery is delayed. If, on the other hand, the infection prove a fatal one, no rise may take place in the opsonic index. Chart I. illustrates these various types of curve.

It must, however, be admitted that this is but a rough



TYPES OF REACTION OF THE OPSONIC INDEX IN PNEUMOCOCCIC INFECTION. (After Eyre.)

(a) Immediate, as seen in mild diseases ; (b) delayed : and (c) progressive decline, as seen in severe and fatal infections.

generalization. It represents the sequence of events commonly encountered in acute infections, but exceptions are sometimes met with. Thus, in chronic infections, an index constantly above the normal may be encountered ; and in acute infections the index may attain a very high level, and continue to rise, while the clinical condition of

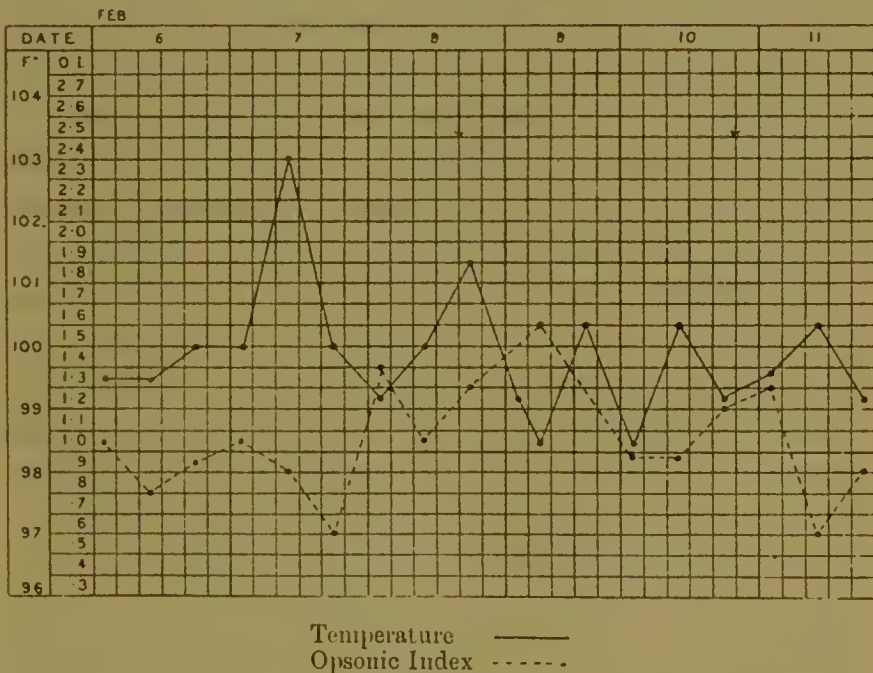
the patient is steadily becoming worse—a state of affairs sometimes met with in acute cerebro-spinal meningitis. For this the following explanation has been offered: Recovery depends, not on the amount of ‘immune bodies’ present in the blood, but on the amount that is carried to the focus of infection. If there be at this site free circulation of the body fluids, lymph, and plasma, the phagocytes are easily able to deal with the sensitized bacteria; but should this flow be interfered with or deficient, then the bacteria hold the upper hand. To compensate for the deficient circulation, the body makes endeavour to produce further excess of opsonin—an endeavour which may have a successful result, or may end in failure.

This affords a satisfactory explanation of such events as these: (1) A case of cerebro-spinal meningitis progressing to a fatal issue, with an index perhaps as high as 20. The high intraspinal pressure characteristic of this disease effectively bars the way to the ingress of lymph richly laden with immune bodies, and only by the removal of large quantities of cerebro-spinal fluid, possibly entirely devoid of protective substances, can recovery be aided. (2) The case of a chronic abscess making no obvious attempt at recovery, despite an opsonic index of the blood-serum towards the infective agent of above the normal. Here we find a thick-walled cavity lined with fibrous tissue and coagulated lymph, within it dead phagocytes, many bacteria, and a fluid under pressure, and perhaps entirely devoid of opsonin. The access of immune bodies from the general circulation is a practical impossibility, but the body makes a brave fight; and in the hope that some may filter through the abscess wall, maintains the immune bodies at as high a level as it can.

The accuracy of this view is supported by the change in clinical condition, brought about in such a case by the liberation of the pus, scraping of the thickened wall, and by flushing of the cavity with fluids which promote osmosis of the tissue fluids.

Cases such as the above, so far, then, from negating the view that a high content in opsonin of the serum is

CHART II. (A. C. INMAN.)



This chart shows how temperature and opsonic index were correlated in a case of pulmonary phthisis. The two will be seen to have moved together, but in reverse directions, a more or less constant phenomenon.

conductive to recovery, and a low content to chronicity or death, afford strong confirmatory evidence of its accuracy. Inasmuch, however, as there are many other factors beside opsonin concerned in the production of immunity, it by no means necessarily follows that even thorough flushing of an infected focus with fluid rich in opsonin

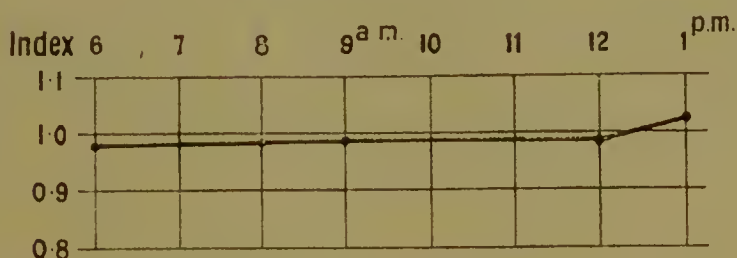
will suffice for recovery. For instance, in acute miliary tuberculosis the opsonic index is often very high, and there does not appear to be much obstacle to the flushing of the infected parts with richly-laden plasma, yet the issue is usually a fatal one.

We must now pass on to the consideration of another class of case, in which the opsonic index pursues a curve very different to those already dealt with. For instance, if reference be made to Chart II., which shows the course of the opsonic index as determined thrice daily in a case of pyrexial phthisis, it will be seen that the curve is a very irregular one, sometimes assuming a position well below the normal, sometimes one well above it. This type of curve is one by no means infrequently encountered, and especially apt to be found in cases of pulmonary tuberculosis, and it is highly important to learn its significance. Now, it has been found that if a case like this be confined to bed, with absolute rest, the excursions of the opsonic index are much diminished, so that ultimately a position may be assumed which is more or less constant, and even fall within the normal limits. If now this patient be allowed to take exercise, it will be found that excursions of the opsonic index are at once induced. This is well illustrated in Charts III. and IV., Chart III. being that of a tuberculosis individual at rest, Chart IV. that of another who had taken walking exercise between 9 a.m. and noon, and had rested from noon to 1 p.m. in a long chair.

Full consideration of the import of such fluctuations in pulmonary phthisis will be given in the chapter devoted to infections by the *B. tuberculosis*. It suffices for our present purpose to state that this fall during exercise and the succeeding rise during rest is attributed to auto-

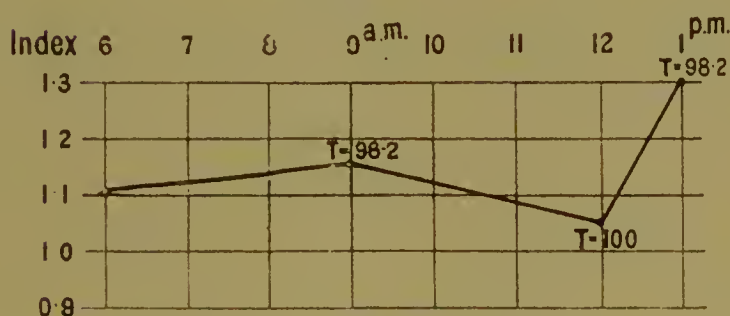
inoculation of the patient by the products of the tubercle bacilli present in the infected foci, and that in all cases of bacterial infection in which the index shows fluctuations

CHART III.



Case No. 7. D. H. Resting. October 4.

CHART IV.



Case No. 4. R. C. Walking. October 11.

from hour to hour it is considered that the process of auto-inoculation is in evidence.

THE OPSONIC INDEX AS AN AID TO DIAGNOSIS.

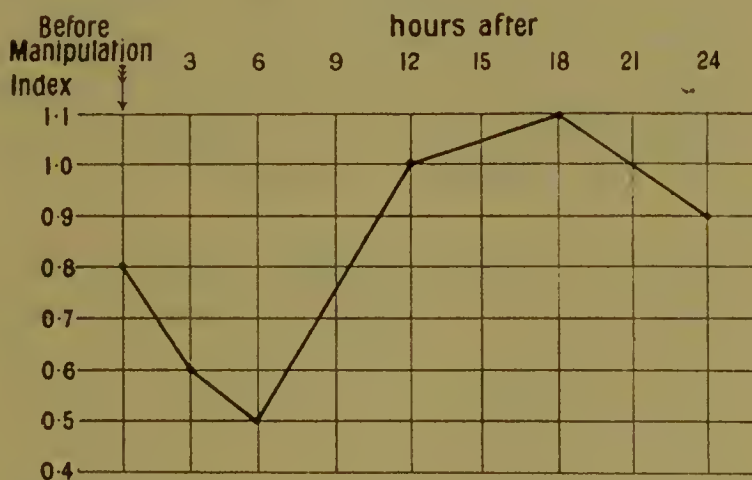
We have now seen that in the course of all infective diseases it is highly probable that at some time or another the opsonic index may fall within the normal limits. It therefore follows that if a single estimation be made in a case of suspected bacterial infection of the index of the serum to the organism in question, and the value be

found to lie within the normal limits, infection by that organism is not necessarily excluded. A series of observations, made at stated times on successive days, is required before any definite conclusion can be reached. If each value so obtained lies within the normal limits, the probability of the organism in question being concerned actively in the production of the disease is considerably minimized. It is, however, not yet entirely excluded from consideration ; for, as we have seen, variations in the index are dependent upon the process of auto-inoculation, and this may be in abeyance during the period of our observation. Recognition of this fact led Freeman to try whether auto-inoculative processes could not be induced in such cases either by active or passive methods. The results obtained were both interesting and highly important, inasmuch as they afford the explanation of the good effects produced by such therapeutic agents as massage, radiant heat and light. An inflamed knee-joint suspected to be infected by the gonococcus was massaged, and blood specimens, taken prior to treatment and at intervals thereafter, were subjected to examination. It was found that a reaction was produced in the gonococcal index precisely similar to that which we have seen to supervene upon infection—in other words, very soon after the massage there occurred a fall of index, succeeded shortly by a corresponding rise to a level higher than that which originally obtained. The fall is to be attributed to the dispersion into the blood-stream of the bacilli or their products, the subsequent rise to the reaction of the tissues to this artificial stimulus. Similar results were obtained after massage of glands in the neck, in which there was doubt of the nature of the enlargement. The curve of the index to the *B. tuberculosis* indicated the correct

diagnosis. Chart V. shows a curve I obtained after careful manipulation of a hip of a child aged six years, in whom the diagnosis of tuberculosis could only be tentatively made by ordinary clinical methods.

As a result of numerous such observations, it now appears that auto-inoculations follow upon all active and passive movements which affect a focus of infection, and upon all vascular changes, no matter how induced, whether by poultices, Bier's bandages, radiant heat, X rays, radium, or Finsen light, which activate the

CHART V.



lymph-stream in such a focus; that surgical operations upon infected glands, joints, or bones, and passive extension and movement of infected joints induce similar changes.

As a method of diagnosis, auto-inoculatory procedures are of wide applicability. For instance, Matthews has utilized it to ascertain the true infective agent in bacterial diseases of the colon. From a specimen of the faeces a thin emulsion is prepared, and cultures made on plates of neutral red bile salt agar. The red colonies are

picked out, and planted in various sugar media to facilitate the isolation of the different species. When pure cultures of the various organisms have been obtained, the index of the serum to each is ascertained. Usually, considerable divergence from the normal is found as regards one or two varieties. These are then held to be the infective agent or agents. If the index in one case is above normal, and in the other case below it, the body is considered to be immunizing itself satisfactorily as regards the former, but to be failing to do so as regards the latter. Confirmation of these views is sought in the following way: The colon is carefully massaged, and the opsonic indices again taken at intervals for the various organisms. If evidence of auto-inoculation having been produced by any organism is found, this is taken to indicate the probability that this organism is concerned in the disease process.

Similarly, in *pyorrhœa alveolaris*, where the bacterial flora is apt to be a very mixed one, the index is estimated towards such bacteria as can be cultured. The gums are then well massaged with the finger-tip, and re-estimation made of the indices towards the various organisms isolated, or at least to those which in the first instance gave values outside the normal limits. Auto-inoculative effects, especially in regard to an organism for which the index as first determined was subnormal, is held to be indicative of an ætiological significance of that particular microbe. The results obtained by this method are sometimes both interesting and of considerable practical value. Unfortunately, its application is much restricted by considerations of time and money, inasmuch as many indices have to be determined with considerable accuracy.

A third method of employing index estimations diag-

nistically is based upon the difference in manner of response of the individual to the therapeutic inoculation of moderate doses of two vaccines, one of which corresponds to the bacterial agent whereby he is infected, the other to a variety of microbe with which he is not infected. The way in which the body responds to therapeutic inoculation will be fully considered later, and it will suffice to say that the injection of an uninfected individual with a moderate dose of vaccine results in little or no depression of the opsonic index, and but a slight subsequent rise, whereas the injection of an infected individual with a moderate dose of the corresponding vaccine results after a short interval in a more or less marked fall of index, which, after a variable period—it may be of hours or it may be of days—is succeeded by a more pronounced rise, which raises the index to a higher level than that at which it stood originally. These facts may be utilized in the following way: Suppose, for instance, it is in question whether an inflamed knee-joint is infected by the *Streptococcus rheumaticus* or by the gonococcus. A dose of 25,000,000 of each vaccine may be given, and samples of blood taken at intervals of six, twelve, twenty-four, forty-eight, and seventy-two hours, the indices being estimated for each organism in each sample. If little or no disturbance of the gonococcic index be detected, whereas the streptococcic, which originally stood at 0·8, gives, say, the following readings—0·7, 0·6, 0·7, 0·9, 1·2—the deduction may fairly be made that the infective agent is the streptococcus, and not the gonococcus. If such a reaction be not found for either organism, then both are out of court, and a fresh diagnosis must be considered.

Similarly, a case of doubtful infection by the *B. tuber-*

culosis may be diagnosticated by observing the course taken by the index curve after the administration of a dose of tuberculin—say, 0·00002 to 0·00005 c.c. of T.R. or bacillary emulsion. In the healthy individual no obvious effect will be produced, whereas in the infected a fall and rise will be produced in sequence.

Brief reference may here be made to the question whether a subnormal index always points to an infection. Whereas in the generality of cases this deduction may be fairly made, instances are on record where a persistent markedly low index appeared to be entirely dissociated with any infection. For instance, Dr. J. W. Eyre and Dr. C. Pryce Jones both had normal indices to the tubercle bacillus before contracting severe attacks of Malta fever. In both instances a very marked lowering of the index to the tubercle bacillus was subsequently noticed. In Dr. Eyre's case it remained at about 0·4 for a considerable period, yet there was no evidence whatsoever of his having been infected by tuberculosis. The explanation of this phenomenon may be found in the observations of Hektoen and Ruediger,¹ and of Yorke and Smith,² of the existence of many bodies, some specific, others non-specific, which have the power of inducing a marked general fall in the opsonic power of the blood-serum, and are therefore known as 'anti-opsonins.' Although such has not been demonstrated to be the case, I yet believe that toxic substances absorbed from the bowel act in this manner. I have observed in persons whose index to the staphylococcus is quite normal that a day or two's constipation would inevitably induce an attack of acne or of furunculosis, and that the staphylo-index was then sub-

¹ *Journal of American Medical Association*, May, 1906.

² *Biochemical Journal*, 1906, p. 341.

normal. I have, however, not had an opportunity of establishing that the fall of index is antecedent to the bacterial infection, but this I strongly believe to be the case. It is therefore probable that a subnormal index may be indicative of a mere predisposition to infection as well as of actual infection by an organism.

The converse question also needs consideration. Is a high index synonymous with the existence of an infection? Here, again, it is hardly wise to give a too dogmatic answer, but it may be said that an index of 1.3 or over is probably almost always a sign of infection, either active or of recent occurrence.

THE OPSONIC INDEX AS A GUIDE IN PROGNOSIS.

The following two theorems may be safely assumed : (1) A low index denotes lack of immunizing response, and unless other protective mechanisms suffice to turn the scale or the index assume a higher level, chronicity or death is indicated ; (2) a high index denotes an attempt to establish adequate immunity. The attempt may fail for various reasons, such as these : the copious supply of opsonin cannot reach the infected focus (see pp. 59, 60) ; the chief defensive mechanism of the body against this particular organism may not be that of phagocytosis, but may, for instance, depend on lysis, in which event it will matter little that opsonin is more than adequate if lysin is seriously in defect ; or, again, while the actual extinction of the infection may depend almost entirely on phagocytosis, this defensive mechanism may not normally be called on till late in the disease. Meanwhile the body has to combat the liberated toxins by the elaboration of the corresponding antibodies. This is what occurs, for

instance, in pneumonia and diphtheria. It thus follows that death may occur from defective antitoxin formation, although the supply of opsonin be more than adequate to do its work if and when called upon. Despite these possibilities, it yet remains that a high opsonic index is, as a rule, indicative of a simultaneous elaboration of the other antibodies, and is conducive to recovery.

Meakin and Wheeler have made a study of the opsonic indices of tuberculous patients undergoing sanatorium treatment, and have found that the case with an index constantly below unity is the one that becomes chronic, and while it may recover to a certain extent, can only maintain that degree of recovery by living under the most favourable conditions, whereas the case with a steady index of unity or over is the one which makes complete recovery if favourable conditions are maintained for a sufficient time. As we have seen, an oscillating index is indicative of auto-inoculations. If these can be controlled and guided, their influence may be all for good; but should they prove uncontrollable the ultimate end is certain death. The bearing that the type of curve has upon prognosis in pneumonia has been indicated already (see Chart I., p. 59).

Such is the more or less general import prognostically of the various types of index in cases which are to be left to natural cure. The matter may, however, be regarded from another aspect—viz., what prognostic bearing has a high or low index when specific treatment is to be pursued? Are we to expect more good to accrue to a case with a high initial index from a course of vaccine treatment, or to one with a low initial index? This is by no means an easy question for a decisive answer. As has been already stated, a persistently high index is by no

means incompatible with a chronic infection, especially if the immune bodies cannot find access to the infected foci. It may be that the protective mechanism of the body is working at highest pressure. Any attempt to raise the pressure further may only burst the boiler unless a safety-valve be fitted. This question will be considered in fuller detail later. It must suffice here to say that the immunizator's work does not consist merely in the injection into the body of measured doses of vaccine at measured intervals. It behoves him to take thorough survey of the whole defensive mechanism, to relieve undue strains, and bring his forces to bear where they are most required. It by no means follows that a high initial index cannot be raised further without advantage to the patient, but there is a real danger in overstimulation, and it is well first to learn whether attention to local conditions may not sufficiently determine the flow of lymph, already rich in immune bodies, to bring about spontaneous cure. Finsen light, as has been already mentioned, is such an agent which produces hyperæmia and promotes lymph flow. Bulloch's experience that the cases of lupus which do best under Finsen light treatment are those with indices of unity or over, whereas those which do worst are those with indices below 0·8, is therefore perfectly easy of understanding. *Per contra*, Bulloch found that the cases which profited most from tuberculin injections were those of the latter class. This, I think it will be admitted, is the experience of most immunizators, and it is only logical to suppose that this is what in theory should be expected in all classes of infection. A case with a low opsonic index is, within certain limits and with certain reservations, more likely to profit from a course of vaccine treatment than one with a persistently high

index. It is, however, well, whenever possible, to defer the giving of any definite prognosis until such time as the precise nature of the infection has been elucidated and the effect of two or three doses of vaccine been determined. For not only, as we have already seen, may the chief defensive mechanism of the body consist, not in the elaboration of opsonin, but in that of other immune bodies whose formation cannot be stimulated to any appreciable extent by any dose of vaccine, but, alternatively, the defensive mechanism may be exhausted, and further stimulation may only precipitate the inevitable end.

In the case of fluctuating indices, inoculation may be quite unnecessary in those instances in which rest and other ordinary therapeutic measures induce a steadying of the index at a reasonable level, at all events till such a time as auto-inoculations can no longer be induced at will. When all attempts at limiting auto-inoculations by rest, etc., appear to fail, therapeutic inoculations of vaccine sometimes achieve a most striking result ; but giving any prognosis in cases where the index makes wide excursions is an injudicious procedure. Far better is it to wait and see.

THE OPSONIC INDEX AS A GUIDE IN TREATMENT.

If the opsonic index is to be utilized as a guide in the conduct of therapeutic immunization, it is obviously necessary that a satisfactory answer may be given in regard to the following provisos :

1. That the opsonic index can be estimated with sufficient accuracy. This, we have seen, is possible in competent hands.

2. That the opsonic index affords a reliable guide as to

the progress of immunization. This we have seen to be the case in the majority of instances, but that numerous exceptions exist, due as a rule to some disturbing influence, such as those already instanced (pp. 60, 61, 69, etc.). We have seen, too, that in those infections in which the main defence of the body consists in the elaboration of antibodies other than opsonin, the curves of formation of opsonin and the other antibodies run a roughly parallel course.

3. That an index curve unfavourable to the patient and to the application of therapeutic inoculation can be modified at will. This, unfortunately, cannot always be accomplished. In a case of phthisis with wildly fluctuating index, the auto-inoculatory process can sometimes be limited by means of absolute rest and increasing the coagulability of the blood, but at other times no influence that can be brought to bear will prove adequate. In septicæmic cases, apart from treatment directed to any local focus of infection and the elimination of toxins from the body, we are practically powerless to limit the auto-inoculations. Practical experience has, fortunately, shown that too much heed should not be paid to failure in this direction as a contra-indication to vaccine treatment.

4. That from the curve of index at our disposal we can deduce with sufficient accuracy the position of the index at the time of inoculation. The determination of the index is a lengthy procedure, and it is obviously impossible for us to know for certain its precise value at the same time as we are performing the inoculation. If the curve has been pursuing a constant course, the value at any given time may be deduced with reasonable certainty, but if the curve be an irregular one, this cannot be done. The usual procedure, therefore, is to take a

blood sample and inoculate at the same time, in the hope that the position of the index determined subsequently may be that anticipated. In this disability lies the great obstacle to the employment of the opsonic index as a reliable guide in treatment. The futility of making occasional determinations and deducing therefrom the whole progress of immunization will be at once admitted by an unbiassed mind. The possibility of making sufficiently frequent observations to be of real value in any serious infection is limited both by the time at the disposal of the physician and the length of pocket of the patient, while in cases where frequent estimation is not required, other methods of control are at our disposal.

5. That, granting that we can deduce with reasonable certainty the precise position of the index, we have in the administration of a vaccine means of influencing it at will. Before any answer can be given to this question, it is necessary to learn the principles upon which the *rationale* of therapeutic inoculation is based, and the effects induced by the administration of a vaccine. The main principles involved, as deduced from numerous observations, are as follows :

(1) 'The healthy tissues of the body elaborate antibodies to any foreign albuminous substance introduced therein, which is capable of solution in the tissue fluids, and the elaboration of these antibodies is carried on in excess of the amount required to combine with the quantity of foreign substance so introduced.' Now, bacteria are such foreign bodies, and the antibodies elaborated by the tissues are directed both against the bacteria themselves, their anabolic and their katabolic products, and consist of opsonin, lysin, agglutinin, antitoxin, and possibly other bactericidal bodies, in amounts varying

with the kind of bacterium and the responsive power of the tissues.

(2) 'That whereas the responsive powers of the tissues at the foci of infection may be defective, the responsive powers of the healthy tissues in other localities may be more than adequate, the requisite stimulus being, however, lacking.' The introduction of a vaccine into the healthy tissues will supply this stimulus. In Wright's words, the healthy tissues are exploited in the interests of the unhealthy ones. It is the aim of vaccine treatment to supply these stimuli when required, and to the desired degree, and the purport of index determinations is to enable judgment to be made of the correct times at which to furnish the stimulus, and of its correct magnitude.

Before considering the help afforded by index estimations in this direction, it may not be out of place to turn our attention for a minute in a slightly different direction. The precise course of the index in most bacterial infections which terminate favourably to the patient has been sufficiently well determined. Is it to be our aim to rest content with merely imitating Nature, or is the attempt to be made to improve upon her efforts? Theoretically, it would appear wise not to interfere in cases where the infection is running a course which clinical experience indicates as being the one normal to that disease, and destined to terminate to the patient's well-being, and that the objective in vaccine treatment should be to induce such a normal course when failure on the part of the body tissues to induce it naturally is threatening. Experience, however, tends to show that we may aim higher without detriment to the patient, and endeavour to improve on Nature's methods, which, after all, are in

a course of gradual evolution ; that perchance our methods may be anticipatory of those which Nature herself will follow some thousands of years hence. The attempt, therefore, to induce on the second or third day an artificial crisis in pneumonia, which normally would not occur till the seventh or eighth, or an immediate defervescence in typhoid fever, which would otherwise be delayed for many days, may therefore be justified, and practical experience, so far as it goes, does not contra-indicate the procedure.

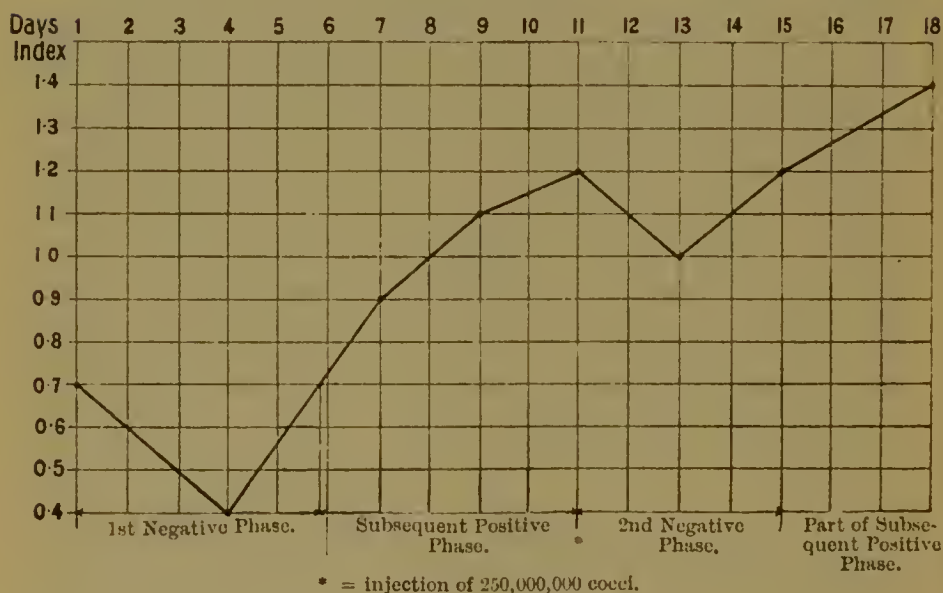
Generally speaking, however, the attempt is made to imitate natural processes as far as possible, and we will now consider what lessons are to be learnt in this direction from index estimations. In acute infections which terminate favourably we have seen that, after an initial fall of index, and its maintenance at this reduced level for a variable period, a steady rise is initiated, and proceeds with considerable rapidity and without remissions. The study of the tissue responses to artificial stimulation teaches us that the steadiness and rapidity of the rise are dependent on the magnitude of the stimulus and the frequency of its application.

The administration of an exceedingly small dose of vaccine may result even within an hour in elevation of the index without any precedent depression. The response is speedy, but its magnitude is small and its persistence of short duration. After a variable period—probably of only a few hours—reversion occurs to its former level. Natural immunity probably depends on such slight stimuli being applied at such short intervals as to be almost continuous. Imitation of this process is obviously impossible in practical medicine, and recourse must be made to higher dosages, which will elicit more marked and more persistent responses. When the dosage

attains a certain magnitude, dependent on the nature of the organism and the responsive powers of the individual, it is found that the effect is different. No longer does an immediate rise in index follow, but there is an initial depression in its value. To this Wright has applied the term of 'negative phase.' The duration of this varies with the dosage. It may be only hours, but it may be days or even weeks. The index then rises, usually with a rapidity greater even than that with which it fell, this period of rising index being termed the 'positive phase.' When the full rise has been attained, which may carry the index to a level considerably higher than that at which it stood originally, this may persist for a variable period, after which a fall, usually slow and gradual, begins. This cycle of changes closely resembles that which we have seen to take place naturally in acute infectious processes, the usual differences being—(1) that the 'negative phase' is of shorter duration than that which we have seen results from natural infection; (2) that the maintenance of the 'positive phase' is relatively a short one. These differences are due to the fact that we have applied a maximal stimulus, the 'negative phase' has been produced with great rapidity, and the 'positive phase' has followed quickly on it. The short duration of the latter is attributable to the employment of a single stimulus. If now this stimulus be repeated, the resultant effect will depend upon its time of application. If this be during the period of 'negative phase,' obviously an acceleration will be produced in the rate of fall; if, however, it be during the period of 'positive phase,' the effect will be the resultant of two opposite forces—the one due to the upward stimulus of the former inoculation, the other to the

initial depressing stimulus of the second inoculation. If the former be the stronger, there will merely be a de-acceleration in the rate of rise ; if the latter be the stronger, as usually proves to be the case, the rise will be transformed into a fall, and a new negative phase, differing, however, in its level, magnitude, and duration, will be induced. After a varying interval a fresh 'positive phase' will be entered upon, which should carry

CHART VI.



the index to a higher level than that attained after the first inoculation. This result is known as the 'summation of positive phases,' and is represented in Chart VI.

By this procedure we substitute large stimuli at infrequent intervals for Nature's small, oft-repeated stimuli, and achieve a high level of immunity by a series of large rises and small falls in place of a steady uniform rise.

In order to produce the best effect, it is therefore neces-

sary that the second stimulus should be applied before the first one has become exhausted—in other words, while the momentum of the upward rise will almost suffice to neutralize the downward momentum imparted by the second inoculation. To delay until the fall from highest level has begun will obviously result in a greatly accelerated fall, which may carry the production of opsonin to a lower level than has been previously reached. Great difficulties present themselves in the achievement of this ‘summation of positive phases,’ difficulties not only of estimating the appropriate stimulus—*i.e.*, the appropriate dosage—but more especially of determining the appropriate time for reapplying the stimulus; for this the impossibility of determining the index with sufficient frequency and of ascertaining it at the precise moment of applying the stimulus is accountable. The task is much easier with some organisms than with others. In the case of the staphylococcus, for example, it is not particularly difficult; in the case of the *B. tuberculosis* it is almost impossible of achievement, and the attempt is given up in favour of the production of a number of separate immunizing responses, each independent of one another.

The deductions made from observations of the index in regard to the magnitude of a given stimulus may be schematically displayed as follows:

Index 12 Hours after Inoculation.	Index 3 Days Later.	Deduction.
Slight fall.	Further fall.	Dose too large.
Slight rise.	But little altered.	Dose too small.
Slight fall <i>or</i> rise.	Marked rise.	Dose correct.

As treatment progresses, it is usually found that a gradual increase in dosage requires to be made at intervals,

in order to maintain adequate responses. So long as these are made it is inadvisable to increase the dose employed, but as soon as they fail, an increase of 50 to 100 per cent. in dosage is indicated.

SUMMATION OF NEGATIVE PHASES.

Just as it is possible to produce a 'summation of positive phases,' so it is possible to produce a 'summation of negative phases.' It is only necessary to repeat an inoculation during the period of negative phase in order to produce this effect. Theoretically, it should be possible in this way to cause practical extinction of immunity, and to whole-hearted adherents of the opsonic theory it must be difficult to understand how this result is not induced by the therapeutic administration of tuberculin on the Continental principle. That some such result was brought about by the reckless administration of tuberculin in its earliest days is a recognized fact, but it requires explanation why such a result is not induced even now by the procedures still in vogue. Various alternatives present themselves :

1. A persistent marked depression of the opsonic index is maintained throughout such a course of treatment, but inasmuch as the defensive mechanism of the tissues against the tubercle bacillus depends mainly on the elaboration of antibodies other than opsonin, compensation is made in other ways for the resultant defect of opsonin.

2. That the depression of the opsonic index is not maintained. The tissues make response to the inoculations in such a way that large doses no longer suffice to depress the opsonic index, but, on the contrary, may only

suffice to act as gentle stimuli. This may be brought about by the elaboration of antituberculin bodies, which neutralize the constituents of the tuberculin concerned in the opsonin reaction, or by the cells themselves being rendered insensitive to the stimulus. If we co-ordinate with this change the continued power on the part of the tissues to respond to the repeated stimuli by the elaboration of antibodies more intimately concerned in the defence against the tubercle bacillus, the success attending tuberculin treatment conducted on these lines is not difficult of comprehension.

The view is steadily gaining ground that it is easy to overestimate the significance of the negative phase. I myself have several times observed patients making most satisfactory progress during a prolonged depression of the index, and Emery¹ and others have noticed the same thing.

It is probable that a very small opsonin content of the blood will suffice for the sensitization of the bacteria necessary for phagocytosis, and that immunity more largely depends on a mechanism of which as yet we have no comprehension.

The impression will, no doubt, have been received that I regard the opsonic index as a somewhat unpractical and unsatisfactory guide to the administration of vaccines. This is, in fact, the view I do hold. What guides may be substituted for it I do not propose to consider here, but in the sections devoted to each particular infective agent. At the same time, I do not deny that its aid may at times be sought, perhaps with considerable profit. On several occasions I have felt that the opsonic chart might have

¹ 'Immunity and Specific Therapy,' p. 280.

helped me out of difficulty, but at the same time it by no means follows that it would have done so had it been available.

In one direction, however, index determinations have a distinct value. I refer to their use in deciding whether an infection has been entirely overcome or is still active. To this end the attempt is made to induce an auto-inoculation. A knee-joint is massaged, a hip manipulated or active exercise taken, or the lungs are subjected to forced breathing, and index estimations made as indicated on p. 64. If no evidence of auto-inoculation can be obtained by these or by more vigorous measures, the assumption may safely be made that the infection has been overcome ; if auto-inoculatory responses are elicited, *per contra*, the focus remains active. Here, again, other signs may suffice to point to a right conclusion, but in this particular direction the index is probably the most delicate indicator that is at our disposal.

CHAPTER III

THE VACCINE: ITS METHOD OF PREPARATION AND ADMINISTRATION

IF any benefit is to accrue from a course of vaccine treatment, the vaccine, obviously, must be compounded of the appropriate constituents ; this can only be insured if the correct differential bacteriological diagnosis be first arrived at. It is no use employing a vaccine of *B. influenzae* for a pneumococcal infection, nor a vaccine of *B. typhosus* for an infection by a paratyphoid bacillus. When an autogenous vaccine is used (*i.e.*, one made from organisms derived from the patient himself), the risk of an erroneous diagnosis is minimized ; but when 'stock' or 'heterogeneous' vaccines are employed (*i.e.*, vaccines prepared from sources other than the patient himself), there is always an added danger of the true nature of the infection being insufficiently elucidated, and of a vaccine wholly unsuited to the patient's needs being utilized. When I say that the use of an autogenous vaccine minimizes this risk, I do not by any means intend to convey the impression that the mere fact that the bacterium from which the vaccine has been prepared was isolated from the focus of disease is necessarily sufficient proof that it is the true infective agent ; it may merely be a concomitant invader, the true infective agent having escaped detection. The further

possibility of mixed infection being present—*i.e.*, of two or more varieties of bacteria working together to the downfall of the patient—is one that should ever be borne in mind. The first step, therefore, in the preparation of the vaccine is to make a thorough direct examination of such infected material (pus, sputum, urine, fæces, etc.) as is obtainable ; to employ such cultural media as are adapted to the growth of each and every organism that is or may be present ; to secure pure cultures of each, and study their connection with the disease processes fully. Guided, then, by experience, clinical and bacteriological, we are in a position to arrive at the correct bacteriological diagnosis with some degree of certainty, and may proceed with the actual preparation of the vaccine.

It will not, therefore, be out of place if a few short hints are given in regard to these points :

The Procuring of the Infected Material.—Here various precautions, according to circumstances, must be taken to insure freedom from contamination, and that the material may be truly representative of the focal secretion. For instance, *urine* should always be drawn off with a sterile catheter, after thorough cleansing of the external urinary meatus ; the night's accumulation should be drawn off into one sterilized receptacle, that of the day into another. No preservative should on any account be added. *Fæces* should be collected without urinary contamination, and it is well to have specimens of both first and last portions of a motion.

Sputum requires especial care in its collection. Carious teeth, pyorrhœa alveolaris, and follicular tonsillitis, are of such common occurrence that for practical purposes their presence may be assumed in every mouth. The

bacteria associated with these conditions need elimination as far as possible. This is best done by the patient taking these preliminary precautions : A new, moderately hard toothbrush should be procured, dipped for a second or two in boiling water, and placed by the bedside overnight, with a covered jug of well-boiled water and a sterile wide-necked glass bottle. Immediately on waking, the patient brushes the teeth and gums thoroughly with the new brush and the sterilized water, rinses out the mouth, gargles the throat well, and swallows two or three mouthfuls of the sterile water. A cough is then given, and the secretion expelled directly into the sterilized bottle. On no account should specimens be collected without these precautions, and it is very inadvisable that more than one mass of sputum should be expelled into any single bottle. Inasmuch, however, as it by no means follows that the nature of the infection at one focus corresponds with that at another, nor that the specimen so obtained is representative of the secretion at each focus, it is always highly advisable that several specimens should be taken—say one on each of two mornings, and one at some time during each of two days : they should be taken after the due performance of the necessary preliminaries, and each should be deposited in a separate bottle and properly labelled.

Secretion from Infected Tonsillar Follicles or Pyorrhæic Pockets should only be collected after similar precautions have been taken. In addition, the surface of the tonsils or margin of the gum should be cleansed with a plug of cotton-wool moistened with the sterile water. By means of a capillary pipette or a very fine probe, specimens may then be taken from the desired localities ; here, also, it is well to take more than one specimen.

Nasal Secretion may be procured, after cleansing the orifice well with soap and warm water, by passing a sterile swab through a nasal speculum, and lightly rubbing the surface of the middle turbinate bone and opposing septum. If the secretion be plentiful, after cleansing of the orifice, some may be expelled directly into a wide-necked sterile bottle.

Pus may be collected from an abscess cavity by means of a sterile glass pipette, after cleansing the adjacent surface of the skin with a little tincture of iodine. When a sinus is in question, it is always well to cleanse the adjacent skin and neck of the sinus thoroughly, express a little of the more superficial pus, wipe this away with sterile lint or cotton-wool, and then pass a capillary pipette some little way down the sinus.

Eye Secretion.—To insure the absence of contamination from the specimen, it is well to wash the eye out thoroughly with sterile water, then cover it for half to one hour with a sterile pad, so arranged, however, as to permit opening and shutting of the lids. This is removed, and specimens taken with a sterile platinum loop from the lower lid at the inner canthus.

Blood Specimens are best taken by means of a capacious all-glass syringe (25 to 50 c.c. capacity) and wide needle which have been thoroughly boiled. The point of the needle should previously have been well sharpened. A bandage is applied to the upper arm, and the skin of the forearm well rubbed with soap and water, with 5 to 10 per cent. lysol, then with absolute alcohol, and finally with ether. If the upper arm be not first bandaged, this procedure may lead to collapse of the superficial veins of the arm, which may persist for quite a considerable period. Alternatively the skin may be painted well with

strong tincture of iodine. If this be applied for five minutes prior to the vein puncture, risk of contamination is negligible. A suitable vein is then selected. If the congestion be very marked, the bandage should be momentarily loosened, as a very dilated vein is apt to slip before the sharpest needle. Grasping the vein in its course between left thumb and forefinger, the needle-point is then introduced into the vein in the direction opposite to the blood-flow. A peculiar feeling of resistance overcome indicates the puncture of the vessel wall, and the necessity of slightly depressing the body of the syringe, so that the needle may be passed some little distance inside the vein without fear of puncturing afresh the vein wall. The very gentlest withdrawal of the piston should be followed by the appearance of blood within the syringe; forced aspiration is both needless and inadvisable. Twenty c.c. or more of blood may be abstracted in this way without difficulty; a drop or two, if desired, may be allowed to fall on a clean slide for direct examination, but this is almost invariably fruitless. Ten c.c. of the blood should then be added to a flask containing 50 to 100 c.c. of peptone broth, to which 5 per cent. of sodium chloride has been added, as this is said to inhibit the bactericidal action of the blood; 5 c.c. of the blood may be added to a second flask containing 50 c.c. of peptone broth, and 5 c.c. to 50 c.c. of peptone broth containing 2 per cent. of dextrose. These blood mixtures are to be incubated at 37° C., and should be pronounced sterile only when no growth is obtained after three days.

Lung Puncture.—Occasionally in infective lung conditions no sputum is obtainable for bacteriological diagnosis; this difficulty is surmounted in the following way:

A 5 to 10 c.c. all-glass syringe with a strong needle is sterilized by boiling, and 2 to 3 c.c. of peptone broth introduced therein. The skin of the chest wall, over the site at which clinical evidence of infection is obtainable, is sterilized with tincture of iodine, and puncture made into the pulmonary tissues; when the desired depth has been reached, 1 c.c. of the broth is expelled gently into the tissues, and reaspirated as far as possible into the syringe after the lapse of a few seconds. During the operation the patient should cease respiratory movements, to minimize any risk of lacerating the pulmonary tissues. This method has never yet failed to yield bacterial growths from foci in which the clinical evidence of infection was sufficiently strong to justify the procedure.

THE STAINING OF THE SPECIMENS.

The desired specimens having been thus collected with due precautions, our next step is to subject them to direct examination. Preparations should be made, not on cover-slips, but on clean slides *secunde artem*—viz., of the urine specimens a few cubic centimetres are taken and subjected to centrifugalization to concentrate the bacteria. When the upper portion is quite clear, it is quickly poured away; the last $\frac{1}{2}$ c.c. is retained and well mixed with the deposit, a loopful or two is placed on a clean slide, and examined under the $\frac{1}{8}$ -inch objective for the presence of motile organisms. A loopful of blood is now taken from the finger-tip and incorporated with the specimen, in order to furnish albumin for the fixation of the bacteria on the slide (if the urine already contain albumin, this addition is needless); a thin smear is then made, and allowed to dry in the air or incubator. Two

or three additional film preparations are made in a similar manner.

Of the fæces a portion is selected of such a nature as seems most likely to give the desired information, and of about the size of a small marble ; this is well rubbed up in a sterilized porcelain dish, with the gradual addition of sterile normal salt solution, until about 25 c.c. has been added. A loopful or two of this is used for the observation of motile organisms and the subsequent preparation of a smear.

From pus and sputum several preparations should be made without any prior treatment.

Appropriate staining methods are now to be applied to the several specimens—one should be stained with carbol-methylene blue or with toluedene blue ; a second by Gram's method (1 per cent. aqueous solution of neutral red being, perhaps, the best available counter-stain) ; a third should be stained for acid-fast organisms by the Ziehl-Neelsen, or by one of Spengler's methods, if their presence is in question. Other methods, such as those for capsule-staining, may be employed in other specimens if desired, but the above procedure is, as a rule, sufficient. As numerous workers appear to experience difficulty in securing satisfactory preparations by Gram's and by Spengler's methods, I have been requested to describe the technique which has yielded the best results. It is as follows :

Gram's Method.—Materials : A saturated solution of aniline oil (made by shaking up excess of oil well with distilled water and allowing the excess of oil to settle ; to be filtered when used), a saturated alcoholic solution of gentian violet (gentian violet, 5 grammes ; 90 per cent. alcohol. 100 c.c.), Lugol's iodine solution (iodine,

1 gramme ; pot. iod., 3 grammes ; distilled water, 300 c.c.), absolute alcohol, and a 1 per cent. aqueous solution of neutral red. The smears, prepared as above, are fixed by passage three or four times rapidly through the Bunsen flame. They are immediately flooded with the filtered aniline-oil solution, and the alcoholic solution of gentian violet is dropped upon the slide, one drop only at each interval of $\frac{1}{4}$ inch ; this insures proper mixture of stain and mordant, which is allowed to remain on for about two minutes. It is then poured off, the slide washed with running water, and covered with the iodine solution for about fifteen seconds ; this is washed off, and the preparation covered with absolute alcohol, which is replaced by fresh alcohol after two to three minutes. After a like interval the slide is washed with water, held slightly aslant, smear uppermost, and a few drops of absolute alcohol allowed to fall on it. If these are not tinged with stain as they drop off the slide, decolorization is complete, otherwise the washing with alcohol should be resumed. The smear is again washed with water, then treated with the solution of neutral red for forty-five to sixty seconds, washed under the tap, dried gently with filter-paper, and finally by gentle warming over the Bunsen flame. If this procedure be carefully followed, the organisms should be stained a deep violet (in which case they are said to be Gram-positive) or a light red (in which case they are said to be Gram-negative).

Spengler's Picric Acid Method is a somewhat tedious procedure, but yields by far the best results in the detection of the tubercle bacillus. Materials required : Carbol fuchsin (basic fuchsin, 1 gramme ; carbolic acid crystals, 5 grammes ; dissolve in 100 c.c. distilled water, and add 10 c.c. absolute alcohol), a mixture of equal

parts of absolute alcohol and of either Esbach's solution, or a saturated aqueous solution of picric acid, known as the picric-acid-alcohol solution, 15 per cent. nitric acid, and 60 per cent. alcohol.

The process is as follows: The air-dried film is not fixed in any way, but is at once stained in plenty of the carbol fuchsin at a temperature of 40° C. for fifteen to twenty minutes. On removal from the stain it is covered, without prior washing, with the picric-acid-alcohol mixture; after five to ten seconds this is poured off, and the smear treated with 15 per cent. nitric acid for five to ten seconds, then again with picric-acid-alcohol. When the colour has become a light yellow, the slide is well washed with distilled water, carefully dried, washed with 60 per cent. alcohol, then for a few seconds with 15 per cent. nitric acid, and again with 60 per cent. alcohol. Picric-acid-alcohol is applied till the smear is coloured a bright yellow, excess removed by thorough washing with water. By means of very gentle heat the preparation is dried carefully. This is much the most reliable staining method for tubercle bacilli. If they or their 'splitter'—*i.e.*, granular forms—cannot be detected by this procedure, I do not think they will be by Mutch's or any other method.

THE PREPARATION OF CULTURES.

The films stained by the carbol-methylene blue, Gram, and Spengler methods, are carefully examined, and a good idea arrived at as to the probable nature of the infective agent or agents and of the media which will prove most favourable to their cultural growth. Space forbids my entering fully into this question, and reference must be

made to advanced textbooks on the subject. A few points may, however, be referred to :

1. The extreme value of careful observations of stained smears of the material before applying any cultural methods. These may inform us, for example, that in a certain specimen of urine there are large numbers of the colon bacillus, and considerably fewer *Streptococcus longus* ; that in a sputum there are considerable numbers of each of the following : *B. influenza*, pneumococcus, and bacillus of Friedländer. By this we learn that extremely careful plating indeed on media adapted to the speedy growth of the streptococcus in the former instance, and of the *B. influenza* and pneumococcus in the latter, is requisite ; that if possible some method of inhibiting the rate of growth of the very freely growing *B. coli* or bacillus of Friedländer should be employed, or that, in default of this, the culture-plates must be frequently scrutinized with a view to the picking off of colonies of the shyly-growing organisms before they are overgrown by the others. On one occasion I made repeated attempts to isolate a *S. longus* from a urine teeming with *B. coli*, but all in vain, until I thought of adding some highly lytic serum for the latter organism to the urine, and so quite overcame the difficulty.

In the case of the sputum above instanced, success will only attend our efforts if we employ large culture-plates of blood-agar, and inseminate them by means of a series of parallel strokes of a loop laden with a very minute portion of the sputum. After eighteen to twenty-four hours' incubation, there will certainly be no difficulty in picking off colonies of the bacillus of Friedländer, probably none with regard to the pneumococcus, and possibly none so far as the *B. influenza* is concerned :

but if failure attend on any of these, the plate should be returned to the incubator for another twenty-four hours, when a successful attempt may probably be made. Should, however, the rate of growth and relative excess in numbers of the bacillus of Friedländer be such that repeated failure is experienced in securing pure cultures of the pneumococcus and *B. influenzae*, the following device may be adopted: The addition of a considerable amount of Friedländer toxin to the blood-agar medium prior to pouring the plate will inhibit the growth of that organism, but accelerate that of the *B. influenzae*. Accordingly, 5 c.c. of broth is inseminated with the bacillus of Friedländer, incubated for three to five days, sterilized by heating to 63° C. for one hour, and 3 c.c. of this added to 12 c.c. of melted blood-agar. A plate of 5 to 6 inches in diameter is prepared from the mixture, and inseminated in the manner I have indicated with a freshly procured sample of the sputum.

2. That films and cultures should be made from specimens as soon as possible after they are taken. As some varieties of bacteria grow rapidly at air temperatures and others do not, the former will continue growing to the exclusion of the latter, and an utterly false conception of the bacteriology of the condition may be formed.

3. That inasmuch as the bacteria in their habitat in the body have been as a rule growing in a medium bathed with plasma, it is well to provide plasma for their growth in artificial cultures; this may be done by adding ascitic fluid, pleural exudate, or, best of all, human blood, for some bacteria are highly hæmophilic—*e.g.*, the *B. influenzae*.

Mistakes will be largely obviated by making it an invariable rule to employ blood-agar plates as one of our

culture media ; these should be incubated for at least three days before being finally pronounced sterile.

4. That bacteria can be rarely seen in stained *blood-films* ; that in blood cultures their growth may be much delayed by the presence therein of the various antibodies ; that no visible growth or change in the appearance of the medium may be noticeable even after three days, but that the preparation after twenty-four hours' incubation of subcultures on a blood-agar plate will frequently enable an earlier detection of the bacteria to be made.

5. That growth of the tubercle bacillus may, in the great majority of cases, be easily obtained in three weeks direct from the secretion by the use of the 'antiformin' method. The technique which I have found to give excellent results is as follows : 15 c.c. of a 15 per cent. aqueous solution of caustic soda and 15 c.c. of the liquor sodæ chlorinatæ of the B.P. are mixed together, made up to 100 c.c. with distilled water, and kept in a well-stoppered bottle ; this gives a 30 per cent. antiformin mixture. Equal parts of this and of the sputum are placed together in a thick-walled test-tube with a rubber stopper, and mixed by thorough shaking. This is placed in the incubator at 37° C. for one hour. About 5 c.c. of the mixture is then placed in a sterile 15 c.c. centrifuge tube, and centrifugalized at a very high speed for five minutes ; the supernatant liquid is pipetted off, and 5 c.c. of sterilized water added to the deposit, with which it is well mixed. After five minutes' thorough centrifugalization, the supernatant liquid is pipetted off, and this washing operation twice or thrice repeated. The final sediment is employed for the insemination of two or three tubes of glycerine-egg medium (well beaten up egg, 73 per cent. ; distilled water, 25 per cent. ; glycerine, 2 per

cent. Mix thoroughly, tube and inspissate at 80° C. for one hour on two consecutive days, incubate for two days at 37° C., and observe sterility).

Subcultures of the various organisms having been obtained *secunde artem*, it now becomes necessary to determine of which ones vaccines are to be prepared. In this the decision may be arrived at by a knowledge of the results of bacteriological examinations in a series of similar clinical conditions, assisted, if desired, by estimations of the opsonic index towards the various organisms, and by the various serum reactions, agglutination, lysis, and 'deviation of complement' (for which last see Emery's 'Immunity,' p. 168 *et seq.*). Of these the agglutinative one is the easiest of performance, but is not generally applicable; the 'deviation of complement,' much the most difficult to perform, is more generally applicable, and may afford evidence of extreme value.

PREPARATION OF THE EMULSION.

Inasmuch as the immunizing power of a vaccine is in most cases a factor of the virulence of the organism, this being especially the case with hæmophilic organisms, such as the gonococcus, pneumococcus, *B. influenzae*, and streptococcus, it is well, whenever possible, to employ the first pure subculture for the preparation of the vaccine. We will assume that this has been prepared on a blood-agar plate.

We proceed as follows: Two or three drops of sterilized salt solution (1·2 or 0·1 per cent., according to circumstances, which will be referred to presently) are added to the growth, and incorporated with it by means of light strokes with an aluminium rod, the last inch of the distal

end of which has been bent at a right angle ; the salt solution is added drop by drop, with thorough mixing of the growth. When 3 to 5 c.c. have been added in this way, the emulsion is transferred by means of a sterile capillary pipette to a strong, large test-tube, containing a dozen sterile beads. Thorough agitation, either by hand or in a 'shaker,' is performed until there is no sign of clumps of bacteria and the emulsion appears of uniform density. This is then centrifugalized for a minute or two at a low speed, and pipetted off into a sterile Erlenmeyer flask of 50 c.c. capacity, more salt solution being added if the emulsion appear unduly concentrated. It is then ready for the next step, that of standardization.

At times great difficulty is experienced in making satisfactory emulsions of the bacterial growth ; this is especially the case with such organisms as the *M. catarrhalis*, *M. paratetragenus*, and *Streptothrix actinomycosis*, and even when the initial emulsification has been satisfactorily performed, spontaneous agglutination may occur. This may sometimes be obviated by the use of the 1·2 per cent. salt solution, the 0·1 per cent. dilution being that usually employed. When failure persists in attending all our efforts, the only thing to do is to transfer the ill-distributed mixture to the test-tube, and plunge this for a minute or two into a water-bath at 75° to 80° C., and then agitate thoroughly with the beads ; this procedure is frequently successful, and does not appear to impair the vaccine.

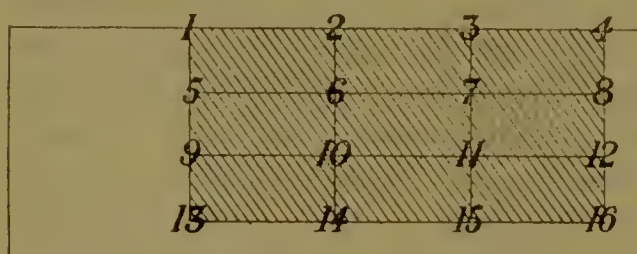
THE STANDARDIZATION OF THE VACCINE.

Three alternative procedures are available—two involve counting the bacteria in the emulsion, the third dispenses with the preliminary emulsification, and is by weighing.

Wright's method of counting is as follows : One end of a few inches of glass tubing, $\frac{3}{8}$ inch in external diameter, is drawn out into a fine capillary thread, which is then cut off, giving a total length of 6 to 8 inches. A rubber teat is fitted to the larger extremity, and a mark made upon the capillary thread about $\frac{1}{2}$ inch from the end. This constitutes the unit volume. The emulsion being ready to hand, the finger-tip is pricked on the dorsum, and a drop of blood expressed. By gently compressing the rubber teat, and then slightly releasing the pressure, two or three volumes of the 2 per cent. citrate solution are sucked into the capillary thread ; then a small bubble of air, next a volume of blood, then a bubble of air, finally a volume of the emulsion. The whole is then expelled on a clean glass slide, and carefully mixed by alternately sucking it up and expelling it upon the slide. This mixing having been thoroughly carried out, the whole is divided into approximately two parts, which are transferred each to a clean slide, and then carefully and evenly spread by means of a spreader. In this way uniform smears are obtained. These are allowed to dry in the air, and stained with Leishman's stain for three minutes. The slides are then flooded with distilled water, which is allowed to remain for fifteen minutes ; this is poured off, and the preparations washed in distilled water till pink in colour, and no more blue escapes into the water, and dried with filter-paper.

They are now ready for counting. By means of a

blue grease pencil the two diameters at right angles are marked upon the ocular of the microscope, so that the field is divided into four quadrants. The counting is thereby greatly facilitated, and is carried out as follows: The smear in the slide is mentally divided up into nine equal areas, as in the subjoined figure. A whole field of the microscope is counted at each of the angles as indicated, so that a total of sixteen fields is counted.



The numbers of red blood cells seen in each field are set down in one vertical column, the

numbers of organisms in another. Each column is then added up, so that the numbers of corpuscles and bacilli respectively in sixteen microscope fields are estimated. This is repeated for the second slide, and the two results added together. These thirty-two fields may be assumed to give a sufficiently accurate count. We will assume that 600 red cells have been counted and 1,500 bacilli. Now, a cubic millimetre of blood contains 5,500,000 red cells, and equal volumes of blood and of emulsion were taken. A cubic millimetre of the emulsion, therefore, contains $\frac{5,500,000 \times 1,500}{600}$, or 13,750,000 organisms per cubic millimetre, or 13,750,000,000 per cubic centimetre.

The second counting method is precisely similar to that employed for the enumeration of the red blood cells; the diluting and staining fluid is made by adding to a 1 per cent. solution of sodium chloride in distilled water suffi-

cient formalin to make 2 per cent., and alcoholic gentian violet or toluedene blue 5 per cent. The Thoma-Zeiss hæmocytometer is employed, and the bacteria allowed to remain in the counting cell for one hour prior to enumeration.

The third method, which has been worked out by Wilson and Dickson,¹ and is applicable to all bacteria, is as follows: The combined weight of a rectangular piece of thin platinum foil ($1\frac{1}{2}$ inches by 1 inch) and of a small dry test-tube is estimated. The bacterial growth is carefully scraped off the surface of the medium and transferred to the platinum foil, which is then replaced in the weighing-tube. The latter is now put in a desiccating chamber, which may conveniently be made out of a strong boiling-tube, to the orifice of which a rubber cork pierced by two glass tubes is fitted. One of these tubes is attached to a Sprengel pump; the other has a well-fitting stopcock, and is connected with a bulb filled with cotton-wool; by this air is gradually admitted when desiccation is completed. The desiccating-tube and contents is then placed in a water-bath at 50° C., and the Sprengel pump set working.

Desiccation is complete in less than fifteen minutes, when air is cautiously admitted via the stopcock, and the glass tube and foil allowed to cool within the desiccator. They are then weighed, and the amount of bacterial growth estimated. The platinum foil is then spread out in a sterile dish, the pestle moistened with salt solution, and the dry growth carefully emulsified, salt solution being added drop by drop. In less than five minutes emulsification should be uniform and complete.

Wilson and Dickson give the following values in round

¹ *Journal of Hygiene*, May 3, 1912, No. 1, vol. xii., p. 56.

figures for the number of bacteria in 1 milligramme of dried growth of the various bacteria :

Staphylococcus	=	3,000,000,000
Streptococcus	=	3,400,000,000
Gonococcus	=	4,500,000,000
Meningococcus	=	3,000,000,000
<i>B. coli</i>	=	6,400,000,000
<i>B. typhosus</i>	=	8,000,000,000
<i>B. pyocyaneus</i>	=	3,400,000,000
Bacillus of Friedländer	=	4,300,000,000
<i>M. melitensis</i>	=	14,000,000,000

They claim that the method is rapid, simple, gives uniform results, and is applicable to all bacteria which grow on solid media, whether they form uniform emulsions or not, and that the subsequent preparation of a uniform emulsion is much facilitated by the rapid desiccation.

The following interesting correlation between the initial doses of the various bacteria and the actual weights may be thus arrived at :

Organism.	Initial Dose.	Corresponding Weight in Milligrammes.
Staphylococcus	100,000,000	0·03
Streptococcus	10,000,000	0·003
Gonococcus	25,000,000	0·005
Meningococcus	10,000,000	0·003
<i>B. coli</i>	25,000,000	0·004
<i>B. typhosus</i>	100,000,000	0·012
<i>B. pyocyaneus</i>	25,000,000	0·007
Bacillus of Friedländer	50,000,000	0·01
<i>M. melitensis</i>	50,000,000	0·0036
Tuberculin T.R.	0·00001 c.c.	0·00002
Tuberculin B.E.	0·00001 c.c.	0·00005

THE STERILIZATION OF THE VACCINE.

The method usually employed for the sterilization of the vaccine is that by heat, the flask containing the emulsion being maintained at a temperature of 56° to 58° C. for thirty to forty minutes. This is best done in a water-bath fitted with a cover, so that all parts of the flask may be subjected to the heat. Inasmuch as this procedure will not suffice to insure sterility in all cases, that of the staphylococcus often proving an exception, it is necessary sometimes that a temperature even of 63° C. should be employed. As, however, excessive heating is to be deprecated, the lower temperature is often utilized, and sterilization completed by the addition to the cold emulsion of some antiseptic such as carbolic acid, 0.5 per cent., or tricresol, 0.3 per cent. When the two have been left in contact for twenty-four to forty-eight hours, careful testing by means of cultures will usually show that no living bacteria are any longer present.

Careful investigation has shown this standard method is by no means always the best one. The researches of Semple and Matson and of Harrison have shown, for instance, that the application even of 53° C. of heat to a vaccine of the *B. typhosus* impairs both its keeping properties and immunizing power. They find that the addition of 0.5 per cent. of carbolic acid to an emulsion causes the death of the *B. typhosus* within twenty-four hours. This also holds for certain other bacteria, but I would point out a source of danger; in many instances the statement needs qualification. The action of antiseptics is a chemical one, and more or less obeys chemical laws; accordingly the influence of mass action cannot be omitted from consideration, and while it is true, for

example, that the addition of 0·5 gramme of carbolic acid crystals to 100 c.c. of an emulsion of *B. coli*, containing, say, 100,000,000 organisms in each cubic centimetre, will insure sterility in twenty-four hours, it by no means follows that the same result will be secured by a similar procedure when the strength of the emulsion is 10,000,000,000 in each cubic centimetre; in fact, it will not be, even if the action of the antiseptic continue for weeks or even months. So far as I have ascertained, the limit for the *B. typhosus*, with a percentage strength of 0·5 c.c. carbolic acid, is reached when the concentration of the emulsion is 2,000,000,000 in each cubic centimetre.

Not only is the antiseptic added to complete the sterility of the vaccine so far as the pathogenic organism is concerned, but also to prevent the multiplication of such sporing organisms as may find access to the vaccine from the air. I say 'prevent the multiplication' advisedly, for in this concentration the antiseptic will not insure their death. As the complete prevention of contamination of the vaccine by air organisms during the many steps necessary for the completion of its preparation is by no means easy, it follows that if small portions of the finished product be well diluted with peptone broth, and incubated at 37° C., living *B. subtilis* or *B. mesentericus* may make their appearance after, it may be, one, two, or three days. The question arises, Does this negative the advisability of using such a vaccine therapeutically? The answer to this is, Not necessarily in the slightest degree. The presence of one spore in the amount of vaccine used for the cultural observation will result after incubation in the appearance of millions of the living organism, and an utterly false conclusion may be arrived at as regards the actual contamination of the

vaccine. The presence of one, a dozen, or even a hundred spores of the *B. subtilis* in a dose of vaccine would matter not one jot, and the view that such contamination is evidence of the unfitness of the vaccine for therapeutic purposes is not necessarily justified ; the cause may lie, perhaps, in the fact that the salt solution used in emulsification had been at some time exposed to the air, and not been resterilized before use. It is, of course, evidence of some lack of care, but to exclude absolutely the presence of all sporing organisms from a vaccine prepared during the height of summer is a very difficult matter. I therefore consider that only the evidence of gross contamination, as determined by the evaluation of the spores by plating experiments on the finished vaccine, should condemn the vaccine. I feel that this is a point of some importance, for if the presence of a single spore is to condemn a vaccine, it must inevitably necessitate the application of such heat or of such amounts of antiseptic as will seriously impair the immunizing power of the vaccine. At the same time, if such a contaminated vaccine is to be employed therapeutically, it is absolutely necessary that the precise nature of the contamination should be determined, both by aerobic and by anaerobic cultures, in order to exclude all possibility of the contamination being that by spores of the *B. tetani*, *B. anthracis*, or other pathogenic sporing organism.

This trouble of contamination is especially apt to arise in regard to those vaccines which require extreme care or special methods for sterilization. As we have seen, a vaccine of the *B. typhosus* is best prepared without the application of any heat. This holds equally for some other organisms, such as certain strains of streptococci and pneumococci. With some strains the application of

heat above the usual amount is essential for the production of good immunizing power; with others this is fatal, and chemical antiseptics are required: 0·5 per cent. carbolic acid, 0·3 per cent. tricresol, or 25 per cent. solution of galactose, may each or all prove satisfactory. In yet other cases, sunlight or radiant light will probably be found to yield the best result. Trial of the various methods alone will tell which procedure is the most suitable.

In some instances vaccines are employed of bacteria which are of full virulence or have been attenuated by exposure to heat insufficient to produce their death. Strong's antiplague vaccine and some anticholera vaccines fall into the former category. Castellani's typhoid vaccine is an instance of the latter kind.

THE TUBING OF THE VACCINE.

The sterility of the vaccine having been secured by the method deemed most appropriate, it remains to store the finished product in suitable receptacles and in graduated dosages.

One point worth remembering is that it is almost impossible to foretell the possible duration of treatment. It is therefore wise—(1) to make adequate vaccine to begin with, lest it be impossible to secure fresh cultures later, although recovery be not complete; (2) not to dilute down the whole of the stock, but to put away in a sealed bottle a few cubic centimetres of full strength, lest the supply of large doses prove inadequate. In past years I should at times have been saved great trouble by recognizing these possibilities.

Let it be supposed that the highest dose contemplated as necessary is 1,000,000,000, and that some of the vaccine

has been reduced to this strength. We now require a stock of 1 c.c. sterilized glass bulbs of different colours—white, green, blue, brown, amber—or else of one colour, and a diamond pencil wherewith to indicate the dosage upon the bulb. A standard burette graduated in tenths of a cubic centimetre is set upright, and to the lower end a piece of glass tubing, so drawn out as to be capable of entering the necks of the bulbs, attached by means of rubber tubing. The emulsion is then poured into the burette, and the tap of the latter opened till a drop appears at the end of the attached glass tubing. Into each of the desired number of white bulbs 0·8 c.c. of the emulsion is placed ; the balance is then run off, diluted with an equal volume of 0·3 per cent. tricresol solution, and returned to the burette, the desired number of 500,000,000 doses being filled into green bulbs, and so on ; the ends of the bulbs are finally sealed in the flame-tip of a Bunsen burner. If a dose be urgently required, a tube containing the desired strength is again sterilized in the water-bath at 54° C. for thirty to forty minutes. After the lapse of two days it is well to re-test the sterility of one of the highest dosages. If living spores are found present, their significance should be adjudicated upon in the way indicated on p. 103.

THE KEEPING POWERS OF THE VACCINE.

The careful observations already alluded to on the permanence of the immunizing power of typhoid vaccine by Semple and by Harrison have shown that various factors are involved therein, and that it is only by the exclusion of all heating procedures that a vaccine can be secured which still possesses full immunizing power after the lapse of a year : similar statements are made

in connection with cholera vaccine. Furthermore, the rapid deterioration of old tuberculin once it has been diluted is also insisted on, especially by German workers. Arguing on analogy, some authorities hold that the same rule must obtain for other vaccines. Sufficient accurate observations on this point are wholly lacking, but clinical observation on the therapeutic action of certain vaccines prepared many years ago not only absolutely negatives the correctness of this assumption, but tends to show that in some cases the immunizing power distinctly rises for quite a considerable period. A possible explanation of this is as follows : Deterioration may only occur in the case of those bacteria in regard to which immunity depends partly or largely upon the elaboration of lysins. When vaccines are kept the bacteria tend to undergo autolysis, and if this process be complete the power of exciting the formation of lysin in the body is thereby lost. In the case of those organisms in regard to which immunity does not depend at all on lysins, but on anti-endotoxins and opsonins, and which only slowly undergo autolysis, keeping results in the gradual liberation into the vaccine of the 'endotoxins' or 'insoluble toxins.' If the endotoxins are liberated more rapidly than they disappear, the rate with which an antitoxic immunizing response is made to the introduction of such a vaccine may be considerably accelerated, for only after lysis of the bacteria by the tissue fluids at the site of inoculation had occurred would the stimulus to the elaboration of these antibodies be otherwise given.

The destruction of the bodies which excite antibody formation being brought about by processes of oxidation and hydrolysis, it is almost inconceivable that any deterioration can be induced by diluting with water and keeping in small sealed bulbs such preparations as those

of tuberculin, which are subjected to such drastic processes in their manufacture. So far as I can see, the only possible disturbing factor consists in the alkaline bodies which may be dissolved out of the glass of the containing bulbs; this I hold to be a possible danger, and therefore consider it advisable to employ, as far as possible, only Jena, or alkali-free glass bulbs for the reception of such vaccines as may undergo deterioration.

THE ADMINISTRATION OF THE VACCINE.

Vaccines are best administered with the aid of a 1 c.c. all-glass syringe, furnished with a sharp platinum-iridium or steel needle. The syringe itself may be sterilized by boiling in distilled water, a needle of the former description in the same way, or by passage through the flame of a spirit-lamp, or that furnished by setting light to a tablet of urotropin. In order to preserve its sharpness, a steel needle should be sterilized by boiling in absolute alcohol, and only dropping it in the boiling water as the glass parts of the syringe are being put together with the aid of sterile forceps.

The following points require consideration: (1) Where and how to inoculate; (2) when to inoculate; (3) the effects, local, focal, and constitutional, of inoculation; (4) methods of administration other than by inoculation.

1. *Where and How to Inoculate.*—As the introduction of a vaccine results, as we shall see, in a certain amount of subsequent discomfort, it is well to minimize this as far as possible. This is done by selecting a site—(1) where muscular contractures are not much in evidence; (2) where there is ample subcutaneous tissue; (3) where clothing does not press; (4) upon which the patient does not rest.

The most suitable localities, therefore, are—(1) the point of the upper part of the chest, at a site about $1\frac{1}{2}$ inches below the centre of the clavicle; (2) high up on the buttock, about 2 inches from the middle line; (3) the side of the abdomen, about 2 inches inside the anterior superior spine of the ilium. Correspondingly, the arm and leg are contra-indicated. The skin at the selected site is painted with tincture of iodine or well rubbed with 5 per cent. lysol or with alcohol and then with ether. The vaccine bulb is to be thoroughly shaken in order to get deposited bacilli into suspension, a very necessary precaution if we are to insure that the full dose shall be administered. By means of a scratch with a file or glass-cutting knife the neck of the bulb is amputated, and the bulb inverted over the needle of the syringe; in this way full emptying of the bulb is insured. When all the vaccine has been taken into the syringe, air-bubbles are expelled therefrom, a good fold of skin taken up between the left thumb and forefinger, and the needle boldly plunged into the tissues. If the injection is to be an intramuscular one, the needle should be inserted deeply at right angles to the skin; if it is to be a subcutaneous one, then care should be taken that it is really done subcutaneously, and that the inoculum is not placed beneath a layer of fascia, as the resultant swelling would then produce a maximum of discomfort. When the needle has reached the desired depth, it is well to see that the tip does not lie within a vein; a gentle attempt at withdrawing the plunger will show if this be the case, in which event the needle should be withdrawn a little and its course slightly altered. The inoculum is then slowly expressed, the needle quickly withdrawn, and the skin just touched with weak antiseptic. Some administrators favour subcutaneous, others intra-

muscular, inoculation. Whether there is any advantage in either from the point of view of excitation to the formation of immune bodies is quite unknown ; probably there is none, but as a rule I think deep inoculations into the muscle tissues of the upper buttock are less painful than subcutaneous ones, especially in spare individuals. If a series has to be given, it is best to make trial of various sites, and finally choose that which seems to suit best.

As the formation of immune bodies is a local matter, it is sometimes possible and advantageous to circumscribe a local lesion with the vaccine, this being deposited at three or four separate sites around the lesion, care being taken that healthy parts of tissue alone are utilized.

2. *When to Inoculate.*—The term ‘when’ in this connection is limited to the meaning of ‘at what time of day,’ the choice of appropriate day being considered elsewhere. As we have seen, the first result of the introduction of a vaccine is a diminution in the amount of antibodies, and consequently a depression of the resisting powers of the individual. It therefore follows that in the case of an ambulatory patient it is well to select such a time for inoculation as will insure the least possible exposure to adverse influences from without during the period of depressed resistance ; in other words, it is best to administer the dose in the evening, either when the patient is on his way home, or after dinner, when he is at home. Especially in diseases of the respiratory tract is it very inadvisable that a visit should be paid to a place of entertainment on that evening ; *per contra*, early retirement to bed is the proper procedure. By the following morning the formation of antibodies will be well advanced, and the risk from exposure to external influences will be minimal. In the case of strictly localized infections, any one time

of day will suit as well as another; and when the patient is already confined to bed, external influences do not enter into consideration. There is, however, another very important factor which will considerably influence the choice of time at which to inoculate; as we shall see later, the determination of proper dosage rests mainly on the observation of such clinical signs and symptoms as temperature, pulse, and local reaction at the site of the lesion, as evidenced by hyperæmia, stethoscopic signs, etc. These reactive indications are quickly produced, and should be of slight severity and short duration; they should be at their height after an interval of between six and twelve hours, and be distinctly subsiding after twenty-four hours. With these facts in mind, the time for inoculation should be so adjusted that the careful clinical observation of the patient is possible when the reaction is at its height.

3. *The Effects, Local, Focal, and Constitutional, of Inoculation.*—The *local effects* produced at the site of inoculation vary considerably, and in this several factors are concerned. Among these may be mentioned—

(1) The nature of the individual and the site of the inoculation. In obese individuals the amount of local reaction is, as a rule, confined to a very slight reddening of the skin for an area of about an inch round the puncture, and slight tenderness, whether the inoculum is introduced into the buttock, abdomen, or chest. In sparse individuals the reaction is always greater, and, especially if the inoculum is placed beneath a layer of fascia, may be considerable, consisting in local tenderness and reddening of the skin, coming on after a few hours, and reaching a maximum in twelve to twenty-four hours, when the pain may be quite acute and the skin have all

the appearance of acute inflammation for an area several inches round the puncture. These symptoms may take two or three days to subside completely; occasionally an indurated spot may be felt for a week afterwards. In such cases intramuscular injections have a decided advantage over subcutaneous ones.

(2) The sensitiveness to stimulation of the patient's tissues. The tissues of some individuals seem to respond more acutely than those of others to inoculation with all foreign albuminous bodies.

(3) The nature and amount of the inoculum. Vaccines which readily undergo lysis or contain toxins, such as those of *B. coli* and *Vibrio cholerae*, as a rule produce a more intense local reaction than those containing only endotoxins. Old tuberculin thus produces a more definite local reaction than tuberculin T.R.

The volume is also a factor. Large volumes produce more irritation than small ones; hence it is well to keep the volumes small—0.5 to 1.0 c.c.

The number of contained bacteria has also an influence—the greater the number the greater the reaction; so also with the content and nature of the added antiseptic.

The *focal effects* are exceedingly important, as we shall see, in the adjustment of dosage and intervals. Within a few hours of the introduction, say into the muscles of the buttock, of an effective dose of tuberculin, marked hyperæmia may be observed around a focus of infection in the iris, skin, or larynx; that a similar condition obtains in a tuberculous lung is evidenced by increase of cough and sputum. Similarly, the administration of an appropriate dose of staphylococcal vaccine in the case of a boil will result in increased hyperæmia around the focus, and perhaps by increased swelling, symptoms which may,

however, subside with great rapidity. With very small doses the focal reaction may be so slight as to escape observation; but I would insist on this, that a focal reaction, in however mild a degree, is essential to curative processes at that focus; they will therefore be dealt with later at considerable length.

The *constitutional effects* may also vary within wide limits. With an adequate, but not excessive, dosage they may consist in a slight headache and feeling of malaise coming on in about twelve hours, and lasting for about the same time; there may be an acceleration of ten to twenty per minute in the pulse-rate, and a rise of temperature of 0.5° to 1.5° F. (see Charts VII. and VIII.). Constitutional reactions greater than these are to be regarded as indicative of excessive dosage; severe headache and vomiting occasionally occur in some people with quite small doses—doses which may have been perfectly well borne on several previous occasions. This is especially apt to occur in the case of females if inoculation be performed within three days of the catamenia, when, as we have seen, there appears to be a general lowering of their resisting power.

I have a lady in my care at the present time who has twice responded to inoculation with very small doses of tuberculin and *Pneumococcus catarrhalis* vaccine respectively by precipitation of the catamenia, and on one of these occasions by severe vomiting. The only comfort to the patient is that the subsequent immunizing response is, as a rule, excellent. In other similar instances which are on record the impending onset of menstruation does not appear to have been responsible, and these cases are to be regarded as ones of hypersensitiveness akin to anaphylaxis. In the October number of the *Journal of*

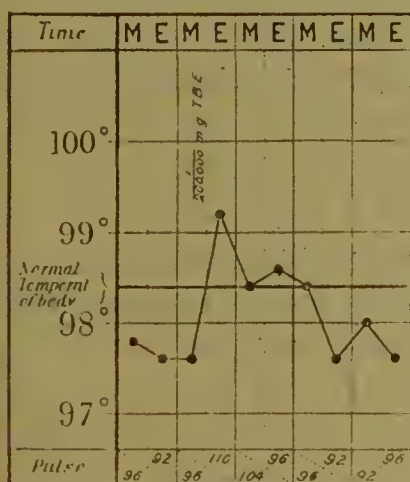
ERRATUM

Page 113.—Charts VII. and VIII. are taken from Dr. Ian Struthers Stewart's article on 'The Vaccine Treatment of Glandular Tuberculosis,' *Journal of Vaccine Therapy*, July, 1912, page 189.

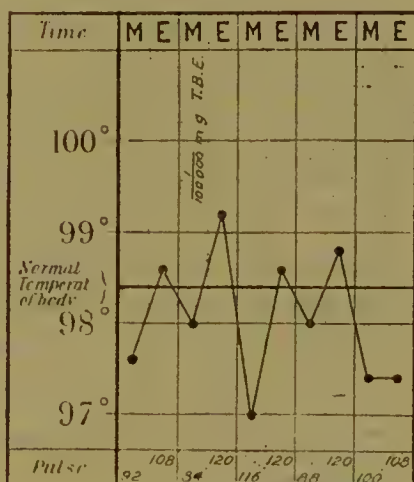
Vaccine Therapy, 1912, a good account is given of an excessively severe reaction, leading within a few hours to a condition of acute pulmonary œdema, and almost the death of the patient—produced, it is true, by a large dose of vaccine, but a dose which had previously been very well borne on several occasions. These severe reactions are fortunately of very rare occurrence.

Other constitutional effects have been noticed. One lady, whom I was treating for acne, responded to quite

CHART VII.



(CHART VIII).



moderate doses of mixed staphylococcus and acne bacillus vaccine by the appearance within twenty-four hours of a skin rash. This was so dusky in appearance that at times the patient said it was almost black. Hardman¹ describes how he himself reacted within a few hours of inoculation with a dose of pneumococcal vaccine by an intense urticaria, which persisted for some time, but eventually yielded to 10-grain doses of calcium glycerophosphate taken thrice daily.

Various attempts have been made to so modify the

¹ *British Medical Journal*, March 25, 1911, p. 726.

vaccine as to minimize the constitutional disturbance. Highly virulent strains appear to be more active in this direction than avirulent ones ; unfortunately the former, as a rule, have much better immunizing powers. In the case of the *B. typhosus* it, however, appears that certain avirulent strains are as active as fully virulent ones, but much less toxic ; such a strain is therefore used for the manufacture of antityphoid vaccine, where the immunizing dose is very considerable (1,000,000,000 to 2,000,000,000 organisms).

Ruffer and Willmore¹ have digested dysentery bacilli with pepsin, and claim that toxic effects are thereby abolished, while the curative and immunizing power is left unimpaired. Gottstein employed a similar process in the preparation of typhoid vaccine, but found that the product was fairly toxic.

Beraneck, by using a peptone-free broth for the growth of the bacilli, and by dissolving out the actively immunizing endobody with orthophosphoric acid, has produced a tuberculin which he claims to be much less toxic than Koch's old tuberculin, and more valuable as an immunizing agent.

Warren Crowe² states that the addition of 0.3 to 0.5 c.c. of a 4 per cent. solution of β -cocaine lactate to a therapeutic dose of tuberculin reduces the constitutional symptoms and period of lowered resistance to a minimum, while not interfering with the immunizing response. The objection to this procedure is that the constitutional reaction is a very important indication as to correct dosage with which we can ill dispense. Besredka treats the bacteria with a serum derived from an animal

¹ *British Medical Journal*, 1908, vol. ii., p. 1176.

² *Lancet*, February 11, 1911.

immunized against that organism, and claims that such sensitized bacteria, when used for prophylactic vaccination, cause a minimal constitutional disturbance and a maximal immunizing response.

The reaction to a considerable dose of vaccine is so much more marked in an infected individual than in the healthy subject that the focal and constitutional reaction is sometimes employed for diagnostic purposes when there is doubt about the nature of the injection.

This is the principle underlying the diagnostic use of old tuberculin, and also the employment that has been advocated of large doses (500,000,000 to 1,000,000,000) of gonococcus and of *Streptococcus rheumaticus* vaccine as diagnostic agents in cases of chronic arthritis. In infected individuals, focally pain and swelling in the joint, and constitutionally rise of temperature by 1.0° to 2.0° F., acceleration of pulse-rate by ten to twenty beats, and general malaise, are said to result, whereas these are absent in the healthy individual, or in the infected one if the vaccine and infective agent do not correspond.

4. *Methods other than Hypodermic of Administering the Vaccine—Oral Administration.*—Certain considerations may militate against the advisability of hypodermic inoculation. Some people have a quite abnormal psychological distaste to this operation; they declare it is not their will that is at fault, nor the pain that distresses them, yet they simply cannot face it. The only trouble I have had personally has been in the case of three well-known athletes. Each on the first occasion fainted, and on subsequent occasions nearly did so; later this trouble disappeared.

Sometimes difficulty may be experienced in the repeated inoculation of nervous young children, while in the case of adults who strongly react locally it would be well if

the vaccine could be given in some other way, with equally good results. Yet again, when people are on their travels it is not always possible for them to secure the services of a medical man.

Considerations such as these have led to trial being made of the oral route. The objection to this procedure is that accuracy in dosage is completely lost, and that the resultant response by formation of immune bodies is not only deficient in amount, but also defective in kind ; for instance, feeding with vaccines of paratyphoid, typhoid, or dysentery bacilli, may result in the appearance of some agglutinin in the blood without a simultaneous protective immunity ; or, on the other hand, there may be conferred a degree of protection and some formation of antibacterial bodies, but none of agglutinin. Leishman has found that there is no reliance to be placed in the results obtained by the oral administration of anti-typhoid vaccine.

The formation of immune bodies in those cases in which estimation can be made of their quantity also proves to be deficient in amount.

On purely *a priori* reasoning, which admittedly may lead to quite erroneous conclusions, it is very difficult to see how, in a patient who is constantly swallowing his own pneumococci, *B. influenzae*, or *B. tuberculosis*, the administration by the mouth of further small doses of his own organisms is going to prove of any use. The results in actual practice, however, show that it is possible, by means of oral doses of vaccine, to influence favourably many bacterial invasions, provided certain precautions are taken. Thus, the stomach must be empty at the time of administration, it must not be affected by catarrhal inflammation, the vaccine must be diluted with

a fluid isotonic with the blood, either normal salt solution or, preferably, fresh horse serum, as there is a chance that the latter may supply some complement of which, perchance, there is a deficiency in the tissues. A furred tongue is held to constitute a contra-indication to administration by this route. As absorption occurs to the greater extent in the stomach and not in the intestines, it follows— (1) that the vaccine should not be given in a keratin-coated pill, or within a membrane which will only dissolve in the intestines; (2) that inasmuch as absorption occurs from the stomach of infants and young children with great readiness, better results should be obtained with them than with adults, especially, also, as the organ in their case is less likely to be affected by catarrh. Actual practice confirms this conclusion, babies and young children responding, as a rule, very well to vaccines by the mouth. I have myself treated infants a few weeks old, suffering from troublesome simple conjunctivitis, which did not yield to ordinary remedies, and from staphylococcal infections of the nose, lip, and body generally, with quite small doses of vaccines by the mouth, and secured satisfactory immunizing responses with great rapidity.

Latham has given the method considerable trial in staphylococcal, streptococcal, pneumococcal, and tuberculous infections, and claims good results. In regard to the last of these, I hold the procedure to be absolutely contra-indicated, both on theoretical grounds and on the results of clinical experience. It is well known that the application of tuberculin to the mucous membrane of the eye results in a marked inflammatory reaction (Calmette's reaction). Is it not reasonable to suppose that the similar application, oft repeated, of tuberculin to the mucous membrane of the stomach and intestines will have a

similar result, and end ultimately in the production of a local condition of greatly diminished resisting power, which may fall before the attacks of the bacilli so freely swallowed? Support is afforded to this view by the observation that the only three instances of acute tuberculous enteritis which I have seen in my phthisical cases during the past three years had all been treated with tuberculin by the mouth prior to coming under my care. In the second place, while it must be admitted that the procedure acts favourably on the temperature in many cases, it does not produce anything like the same amelioration of the focal condition in the lung; in fact, so far as I have been enabled to judge from after-observation of cases which have been subjected to a course of this therapy, the effect upon the pulmonary lesions has been distinctly an unfavourable one. As to why this should be so I can offer no explanation.

The appropriate dose for oral administration appears to be about twice that which should be employed hypodermically.

The rectal administration, as advocated by Calmette and Breton, suffers from all the objections urged against the oral route, and to a much greater degree; it is therefore best left entirely alone.

AUTOGENOUS VERSUS HETEROGENEOUS OR STOCK VACCINES.

It is within the experience of all who practise vaccine treatment that certain cases have obstinately refused to improve so long as a vaccine of alien source was being employed, but immediately responded to one prepared from their own organisms. It therefore becomes neces-

sary to consider how far this militates against the use of such 'stock' vaccines as a routine procedure. The explanation of the above observation is held to lie in the divergency of strain of the bacteria contained in the vaccine, and in the focus of infection. The easiest way of considering the relative advantages of 'autogenous'—*i.e.*, prepared from the patient's own bacteria—and 'heterogeneous' or 'stock'—*i.e.*, prepared from alien bacteria—vaccines is perhaps by arranging them in tabular form.

STOCK VACCINES.

Advantages.	Disadvantages.
1. They are or ought to be composed of strains of <i>proved</i> immunizing powers.	1. They may not contain the strain corresponding to that at the infected focus ; this risk is minimized by compounding the vaccine of as many strains as possible, but if this be done there is a proportionate reduction in the actual number administered of the corresponding strain in a given dosage.
2. They entail less expense to the patient.	2. They may have deteriorated by keeping ; we have already considered this point, and have seen that while this is an appreciable danger in regard to some bacteria, that in regard to others keeping for a certain time may possibly even improve the vaccine.
3. They are immediately available for use in urgent cases.	3. In some cases the difficulty of identifying the infective agent may be greater than that of preparing autogenous vaccines.
4. They are available in cases where it proves impossible to isolate the infective agent or secure sufficient growth for the preparation of an autogenous vaccine within a reasonable space of time ; the former alternative sometimes obtains, for instance, in chronic infections by the gonococcus, the latter in infections by the <i>B. tuberculosis</i> .	

The success attending 'prophylactic' inoculation, which is perforce conducted with stock vaccines, has been well demonstrated in regard to the *B. typhosus*, *B. pestis*, *Vibrio cholerae*, and various catarrhal organisms, and amply justifies the use of stock vaccines for this purpose.

AUTOGENOUS VACCINES.

Advantages.	Disadvantages.
1. The danger of employing a vaccine not compounded of the precise infective agent either as regards variety or merely strain is reduced to a minimum, especially if cultures from several infected foci be employed. 2. As a rule the immunizing power is maximal, and there is no doubt as to the precise dosage given of the appropriate strain or strains; the risk of failure is thereby minimized. 3. It is almost as easy to prepare a large quantity of vaccine as a small one, and if a long series of inoculations is requisite, the cost of an auto-genous vaccine may prove less than that of a stock one in the long-run. 4. Freshness of preparation is insured.	1. Their preparation entails a loss of time which may prove very detrimental to the patient's prospects. 2. The particular strain may from various reasons be defective in immunizing power, and this will only be revealed by the failure of the treatment. 3. The initial cost of preparation is considerable to the patient.

If the 'pros' and 'cons' of each be weighed, the balance of advantage will be found to lie with the 'auto-genous' vaccine—to the smaller extent with such

organisms as the staphylococcus, acne bacillus, and gonococcus; to the greater extent with such as the streptococcus and *B. coli*.

Generalizing, it may be fairly said that in chronic infections little will be lost by trying the effect of a stock vaccine before proceeding to the manufacture of an autogenous one, and that in severe acute infections much may be gained by administering a 'stock' vaccine while the autogenous one is in preparation. It is almost superfluous to add that if a stock vaccine is to be employed great care must be taken in the correct diagnosis of the infective agent, and that to this end due consideration must be paid to clinical and bacteriological evidence alike.

CHAPTER IV

THE RATIONALE OF VACCINE TREATMENT AND SOME CAUSES OF FAILURE

IN the preceding chapters we have learnt—

1. That the defensive mechanism of the body against bacterial invasion consists largely in the elaboration of various so-called antibodies—antitoxin, lysin, agglutinin, opsonin—which respectively act either independently of, or in conjunction with, the phagocytic cells.

2. That the content of the blood-serum as regards these bodies is very frequently a good indication of the progress of general immunity, a high content being indicative of the application to tissues, capable of response, of stimuli appropriate in degree and in time of application ; a low content being indicative either of the non-application of adequate stimuli, or of lack of power on the part of the tissues to respond to such stimuli ; a varying content, now high, now low, being indicative of variable and ill-spaced stimuli applied to tissues capable of response.

3. That at the foci of disease there obtains a condition described by Wright as one of ‘lowered bacteriotropic pressure’—*i.e.*, there is a deficiency locally of immune bodies. Thus, Wright has found that fluid from the pus of a staphylococcal abscess contains little or no staphylo-opsonin, but a full complement of, say, strepto-opsonin ; that the ascitic fluid from a case of tuberculous peritonitis is deficient in tuberculo-opsonin and agglutinin, while

containing adequate amounts of antibodies to other bacteria ; that in typhoid fever the tissues surrounding the rose-spots, the splenic pulp, and ulcerated intestinal mucosa, may be almost entirely lacking in agglutinin, lysin, and opsonin, for the *B. typhosus*.

The true objective of vaccine treatment may therefore be defined as " the determination of the advent to infected foci of adequate antibodies and efficient phagocytic cells."

In a disease process, such as pneumonia, running a normal course to recovery, we see a summation of automatically adjusted stimuli applied to the tissues, and resulting in the elaboration of adequate immune bodies—antitoxin, opsonin, etc.—and of hyperactive leucocytes. At the appointed time free access of these to the infected focus is afforded, the crisis occurs, and recovery follows. But these favourable conditions do not always obtain ; various disturbing factors may come into play, such as the following :

1. The stimuli radiating out from an infected focus may reach the healthy tissues with adequate force, but the antibodies elaborated in response to these stimuli may be unable to gain access to the battle-ground. For instance, in acute cerebro-spinal meningitis sufficient bacteria may meet their end in healthy tissues, and excite adequate formation of antibodies, but these can never reach the infected tissues, owing to the high opposing pressure maintained by the cerebro-spinal fluid.

2. The tissues of the body generally may be able to respond adequately to stimulation, but such stimuli as are being applied are being expended on tissues incapable of further response. This obtains typically in regard to such a condition as progressive lupus of the face ; the infecting tubercle bacilli are rapidly confined to the local

area of infection ; the responsive powers of this are strictly limited, and may become entirely exhausted. Little help is afforded by the healthy tissues of the body, for such stimuli to the formation of antibodies as reach them are minimal in amount.

3. The leucocytes of the body generally may be adequate in numbers and individually efficient. At the focus of disease, however, they may have been entirely worsted in the fight, and the bacterial toxins may have decimated their ranks, and the advent of adequate reinforcements from without may be hindered, or even entirely prevented, by the erection of strong barriers and entanglements. For instance, in the case of a chronic abscess, the pus may contain nothing but dead leucocytes, and the adequate numbers in reserve without are effectually barred ingress by the barriers of coagulated lymph and fibrous tissue which line the cavity wall.

4. The destruction of toxins is not dependent solely on neutralization by antitoxin ; it is also a function of the tissues, especially those of the spleen and liver. Certain quantities are also eliminated unchanged by the skin, kidneys, and intestines. If toxin elimination and destruction, therefore, be inadequate, resultant death from toxæmia may result, despite the elaboration in adequate amounts of other antibodies, and even of the amount of antitoxin normal to that particular pathological condition.

Before we, therefore, take any active part in the conflict, it is necessary to find answers to the following questions :

1. Are adequate quantities of immune bodies already available ?

2. If so, are these reaching the infected foci ? If not, why not, and how is this to be remedied ?

3. If adequate quantities are not available. can we with

advantage exploit healthy tissues in the interest of the unhealthy ones, and insure the advent of the antibodies so formed to the infected foei ?

4. Are the phagocytes deficient or defective ? If so, can this be remedied ?

5. Are toxins being adequately destroyed and eliminated, or does the body require assistance ?

The answers to these questions will be derived partly from clinical, partly from experimental observations, and hence arises the necessity that he who would essay therapeutical immunization must possess clinical as well as immunological knowledge.

Let us therefore see how these answers are to be obtained.

(1) The only means of obtaining a definite answer to this question is by making comparative estimations of the amounts of the various immune bodies present in the sera of the infected individual and of a healthy person respectively. How this is done has been already detailed in Chapter I. As the measurement of some of the antibodies presents great difficulties, it is customary to measure one, the determination of which is comparatively easy, and to assume that the elaboration of the others runs a more or less parallel course with that of the one which has been so determined. For instance, in Malta and typhoid fevers the amount of agglutinin is comparatively estimated, and the elaboration of lysin and opsonin deduced therefrom. In tuberculosis the amount of opsonin is similarly estimated, and the elaboration of agglutinin, lysin, and other protective bodies, inferred. Whenever possible, measurement is made of that antibody which is regarded as playing the most important rôle in the production of immunity.

(2) Laboratory observations having satisfied us on this first point, clinical observation is required to furnish us with the answer to the second question. If curative processes are proceeding with the desired rapidity, it may be assumed that the advent of the antibodies is also satisfactory ; but if healing is delayed, consideration must be taken of the local pathological possibilities.

(a) Is the ingress of the antibodies impossible owing to a high positive pressure at the infected focus ; for instance, is there pus under pressure within an abscess cavity, or peritoneal exudate under tension in the abdomen ?—in which event the obvious remedy is the removal of the pathological fluid by aspiration or an open operation.

(b) Is the abscess cavity or sinus lined by a layer of coagulated lymph or fibrous tissue almost impenetrable by the tissue fluids without ? If so, the obvious remedy is to scrape the walls and irrigate the cavity with a fluid of such composition that it will both decalcify the freshly exuded serum, and so prevent its coagulation, and also, by its high salt content, induce osmosis of fluid to occur through the cavity walls from the tissues beyond. Such a fluid Wright has found to consist of 5 per cent. sodium chloride and 0·5 per cent. sodium citrate in distilled water.

(c) Is the blood-supply to the infected part deficient naturally, is it impeded by the conditions established by the disease, or by the too-ready coagulability of the blood ? In the first and second of these conditions, the application of warmth, either in the form of poultice, hot fomentation, or radiant heat, will promote a freer circulation, while the administration of citric acid in 30 to 60 grain doses, thrice daily, will assist in reducing the too-ready coagulability of the blood.

(d) Are the tissues exposed to constant reinfection

from adjacent parts which are entirely outside the range of attack of the antibodies ? For instance, is the cavity of a pyorrhœic pocket filled with bacteria and cellular débris, or the cavity of a sebaceous gland occupied by a plug of infected sebum ? In the former case, the infected débris must be carefully removed, and reapproximation of the tissues insured by appropriate topical applications ; in the latter case, the infected plug of sebum will require expression.

(3) That an affirmative answer may be given to this question in a considerable proportion of cases, when the antibodies, both generally and locally, are deficient, is evidenced not only by the results of laboratory experiment, but also by clinical observation of the effects of therapeutic inoculation. Failure to achieve these ends is, however, sometimes encountered ; on the one hand, it may prove impossible to incite the formation of the desired antibodies ; on the other hand, it may prove impossible to secure their arrival at the focus of disease.

(4) To secure the answer to this question is not so easy as it might appear. The estimation of the leucocytes in the circulating blood is simple enough, and a leucocytosis is recognized clinically as a favourable sign in many infectious diseases. A general leucocytosis does not, however, necessarily imply an adequate supply of leucocytes where they are required—*i.e.*, at the focus of infection. This still remains to be secured in one of the ways already indicated.

Should the desired leucocytosis not be present, various means are at our command for promoting it, such as by injections of sodium cinnamate ; the leucocytes thus hurriedly cast off from their manufactory, however, appear to have their powers of phagocytosis imperfectly developed.

Again, we have seen that in certain diseases, such as pneumonia, the leucocytes normally exhibit a hyperactive power of phagocytosis when acting in their own serum. Laboratory observations will show whether this hyperactivity be or be not present, but in the latter event we have no means at our disposal for its production.

(5) The answer to this question is best given by the clinical observation of the patient; the condition of the tissues generally, of the pulse (both as regards quality and rate), of the nature of the respirations, of the character of the various excreta (sweat, urine, and fæces), afford valuable indications as to whether toxin destruction and elimination is proceeding satisfactorily. If it be not, stringent measures should be taken to secure this end. Plenty of water should be given by the mouth and subcutaneously, if necessary, to dilute the toxins, and their elimination assisted by the use of diaphoretics, diuretics, and high enemata. Too little regard is, as a rule, paid to the rôle of the intestines as an excretor, not only of toxin, but of the bacteria themselves; thus it has been shown recently that in pneumonia active elimination of the pneumococcus occurs via the intestinal mucosa. Much good is therefore to be anticipated in bacterial diseases from the methodical flushing of the whole lower bowel with saline enemata.

Regard having thus been paid to the more general factors which make for failure or success, it remains to consider the more specific difficulties which are likely to be encountered during the conduct of immunization. These may arise in connection with the vaccine itself, its dosage, or the selection of intervals. The vaccine itself may be at fault in several ways. If a stock vaccine be employed, this, owing to errors of diagnosis, may not be compounded of the right organism,

or of the appropriate strain of the particular organism. This error is obviously less likely to arise in connection with an autogenous vaccine, but, none the less, even here selection may have been made, not of the true infective agent, but of a more or less harmless allied invader. The prior application of the various serum tests will help to obviate this error; on the other hand, the mistake may be rather of the inverse kind: two or more different bacteria may be intimately concerned in the production of the condition; they may have made a joint invasion of the tissues, or one may have trodden on the heels of the other. An instance of the former is an influenza-pneumococcal cold, of the latter a tuberculous ulcer secondarily invaded by a streptococcus; in neither instance is the use of a monovalent vaccine likely to produce a satisfactory result. While the use of needlessly complex vaccines is to be deprecated, I am perfectly convinced that in the employment of insufficiently complex vaccines is to be found one of the commonest causes of failure in vaccine treatment. The vaccine may be at fault in other ways; thus, its method of preparation may not have been such as to develop its full immunizing powers: it may have been prepared from an insufficiently virulent strain, it may have been overheated or not sufficiently heated, it may, perchance, have lost its virtues from overkeeping, or not have developed them fully through underkeeping.

The dosage may be at fault in either of two ways: it may be inadequate, or it may be excessive. In the determination of appropriate dosage the nature and locality of the infection may not have been adequately considered. An acute pneumococcal infection of the lung, with its copious blood-supply, will require the

administration of a dosage very different to that required by a chronic infection of the cornea (*ulcus serpens corneæ*), with an almost negligible supply of lymph. Neglect of this consideration is another most fruitful cause of failure. Experience has taught in regard to dosage what approximately is the one for each bacterium which may be given in the great majority of cases with perfect safety to the patient, and the tendency has been rather to overdo this 'safety play,' and to underdo the 'play to win': this has been responsible for such dosages as 500,000 pneumococci in a case of pneumonia, 10,000,000 *B. influenzae* in a chronic influenza, 500,000 streptococci in pyorrhœa alveolaris, 500,000 *B. typhosus* in typhoid fever, and other such—I almost said—absurdities. There is only one appropriate initial dosage, and that is the dosage, of more or less ill-defined dimensions, which is going to benefit the patient. Unfortunately this dosage cannot be foretold with any certainty, but it certainly does not lie within ultramicroscopic limits. This tendency is, however, in process of decay, and it is becoming better realized that an efficient dosage must necessarily produce some reaction. What constitutes a reaction I have already detailed (see pp. 110-112).

Just as failure may result from the use of inadequate initial dosages, so it may result from subsequent over-dosage. If it be carefully borne in mind that increase of dosage is contra-indicated so long as *any* sign of general or focal reaction is produced, and above all so long as steady progress is maintained, this error will be avoided, provided always that the possibility of fresh infection by some other organism is carefully excluded. The neglect of this proviso I have found a most fruitful cause of over-dosage. I have seen men piling in doses of *B. coli* vaccine

in cases of eystitis from which the *B. coli* had entirely been supplanted by a streptococcus, and wondering why the patient made no progress other than, perhaps, downhill, and found colossal doses of pneumococcus producing no effect upon a new infection by the *M. catarrhalis*.

Failure may also result—but this I find a much rarer occurrence—from the use of improper intervals. It is almost certainly better to wait over-long than to inoculate prematurely, and the bogie of the ‘negative phase’ is ever before the mind’s eye of the inexperienced.

Just as there is some slight difference of opinion among those who adhere to the guidance of the opsonic index, as to whether it is better to reinoculate before the index begins to fall, or to defer the operation until just after the fall has been initiated, so there is a slight difference in the views of those who seek guidance in the clinical symptoms. Some prefer to reinoculate while improvement is still in progress or is well maintained, others to wait for the first signs of retrogression; in other words, some endeavour to produce a summation of positive phases of clinical improvement, others are content with making progress by means of a series of irregular jumps. The former is the more ideal procedure, but is difficult of accomplishment; the latter is less perfect in conception, but is easier of performance and more devoid of risk.

Certainly too short intervals are an occasional cause of failure, but this is usually experienced when advance has been made to the larger dosages. For instance, I have been given in consultation on two or three occasions some history such as the following: A case of aene is treated with a staphylococcal vaccine; after a time improvement ceases with a 100,000,000 dosage at eight-day intervals, but is resumed when the dosage is raised to

250,000,000. This again ceases, and response is made to a 500,000,000 dosage. Ultimately response entirely fails to this dosage, and one of 1,000,000,000 is employed at the same eight-day interval, but now the patient immediately begins to retrogress. The thought at once occurs that the tissues are exhausted, and can no longer make an immunizing response, and several other possibilities suggest themselves; these I do not propose to discuss, but merely state that experience has shown that the tissues were temporarily incapable of response to such oft-repeated stimuli. The 1,000,000,000 dosage is necessary for the production of a response, but this response must not be called for over-frequently; the best procedure is to give the patient a few weeks' rest, then to give a 250,000,000 dose, which will frequently prove quite ineffective. Follow this up by a 500,000,000 dose, and unless this yield an adequate response, proceed after eight to ten days to the 1,000,000,000 dose once more; but, enlightened by past experience, the interval should now be prolonged to one of twelve or even fourteen days.

CHAPTER V

DISEASES OF THE SKIN AND OF THE SUBCUTANEOUS TISSUES

THE interrelationship between various bacteria and diseases of the skin and subcutaneous tissues may be tabulated as follows :

Nature of Lesion.	Variety of Bacteria associated with it.
Abscess	Staphylococcus, streptococcus, pneumococcus, <i>B. pyocyaneus</i> , <i>B. anthracis</i> , <i>B. mallei</i> , <i>B. coli</i> , <i>B. typhosus</i> , <i>B. tuberculosis</i> , <i>Streptothrix actinomycosis</i> , etc.
Acne	Acne bacillus, staphylococcus, streptococcus.
Angina (Ludwig's) ..	Streptococcus.
Bazin's disease ..	<i>B. tuberculosis</i> .
Boils	Staphylococcus.
Carbuncles	Staphylococcus.
Carcinoma	<i>Micrococcus neoformans</i> (secondary invader).
Cellulitis	Streptococci, staphylococci, etc.
Eczema	Streptococci and staphylococci (secondary invaders).
Erysipelas	Streptococcus.
Fistula	Staphylococcus, streptococcus, <i>B. coli</i> , <i>B. pyocyaneus</i> , tubercle bacillus, etc.
Gangrene (diabetic)	Staphylococcus.
Glanders	<i>B. mallei</i> .
Impetigo	<i>Staphylococcus aureus</i> , streptococcus.
Leprosy	<i>B. lepræ</i> .
Lupus	<i>B. tuberculosis</i> (primary), staphylococcus, streptococcus, etc. (secondary).
Nile boil	Staphylococcus.
Oriental sore	<i>Leishmania tropica</i> .
Pemphigus vegetans	<i>Diplococcus</i> (? primary), <i>B. pyocyaneus</i> , staphylococcus (secondary).

Nature of Lesion.	Variety of Bacteria associated with it.
Psoriasis ..	.. Streptococcus and staphylococcus (secondary invaders).
Sinuses ..	.. Staphylococcus, Streptococcus, <i>B. coli</i> , <i>B. pyocyaneus</i> , tubercle bacillus, etc.
Sycosis ..	.. Streptococcus.
Ulcers ..	.. <i>B. tuberculosis</i> , streptococcus, staphylococcus, <i>B. pyocyaneus</i> , pneumococcus, Vincent's fusiform bacillus, etc.
Whitlow ..	.. Streptococcus, staphylococcus.

PRELIMINARY CONSIDERATIONS.

We thus see that the number of bacteria associated with cutaneous lesions in a definitely causal relationship is a large one, while if we include within our list those also which make their appearance as secondary invaders, the greater proportion of the pathogenic bacteria receive mention. In determining the bacteriology of these conditions, this must be carefully borne in mind; for while the therapeutic use of a vaccine directed against a secondary invader may materially improve the clinical condition of the lesion, it can hardly be expected to effect a cure. This, if it can be induced at all, can only be brought about by a vaccine composed of the true infective agent.

We have already seen that *the* essential to the production of a successful issue is, not the mere increased elaboration of the necessary antibodies, but the determination of their advent to the infected focus, and upon the facility with which this can be effected will depend, not only the possibility of bringing about a cure, but also the rapidity of response to our treatment. It is therefore to be anticipated in the case of infections localized in the more superficial layers of the skin or its glands, and therefore almost beyond the reach of antibodies, that

improvement can be induced only with great slowness, that considerable attention will have to be paid to the prevention of reinfection from without, and that assistance will have to be sought from the application of various other therapeutic measures. Typical conditions falling within this category are acne, eczema, and sycosis, and the results of clinical experience are in complete accord with our anticipations. Great attention to details and the prolonged administration of the vaccine are requisite to bring about a successful issue. On the other hand, infections localized in the deeper layers of the corium or in the subcutaneous tissues, such as boils, carbuncles, cellulitis, and erysipelas, are ideally situated from the point of view of vaccine treatment; the blood-supply is copious and easily influenced, and the advent of antibodies to the infected focus readily secured. Prompt response to treatment may therefore be anticipated with confidence, and is, in fact, experienced.

So exceedingly important are these considerations that, at the risk of becoming tedious, I propose to discuss the treatment of the first three conditions on our list—viz., abscess, acne, and Ludwig's angina—at some length, and thereafter merely to indicate the more important obstacles in our path, in the hope that the immunizator will remember for himself that no detail is so small as to be without influence on the production of immunity.

ABSCESS.

Bacteriology.—1. *Acute* abscesses may be produced by any of the pyogenic cocci, and by some which are not usually so regarded. In the great majority of cases one organism only is concerned in the process: occasionally, however, the infection may be a mixed one.

2. *Chronic* abscesses are as a rule due to the *B. tuberculosis*, but secondary infection by other organisms commonly occurs. The *Streptothrix actinomycosis* is occasionally responsible.¹

The exact nature of the infection is to be determined by the direct observation of stained preparations from the pus; by cultural procedures, including anaerobic if aerobic fail to give a definite result; and, if necessary, by the various 'serum tests,' agglutination, lysin, opsonin.

Preliminary Considerations.—1. An abscess may only be a local manifestation of a more generalized infection elsewhere: thus a pneumococcal abscess may be associated with a pneumococcal septicaemia or a chronic infection of the pulmonary tissues; a typhoid abscess with recovery from an attack of typhoid fever, or with a chronic infection of the gall-bladder or kidney. In such cases due heed must be paid to the more important primary focus of infection.

2. In an acute abscess the advent of the antibodies may be precluded by the high positive pressure within the abscess cavity; this will need removal by aspiration or an open operation, whereby the transudation of lymph may be facilitated. Irrigation with Wright's salt citrate solution will prevent subsequent lymph coagulation, and by osmosis maintain the flushing of the infected tissues with fresh lymph laden with bacteriotropic bodies. The dead leucocytes and the tryptic ferment which produces solution of the tissues will also be removed by the aspiration, and healthy leucocytes be attracted and allowed to play their part to greater advantage.

3. In a chronic abscess the walls may be so thickened by deposition of coagulated lymph and the formation of fibrous tissue as to prevent the filtration of lymph from

¹ See p. 171.

without ; this may necessitate the scraping of the walls and the prevention of further lymph coagulation, as already indicated.

4. The local application of antiseptics sufficiently strong to bring about the death of the bacteria within the cavity will almost inevitably result in such damage to the tissues as to render them more susceptible to the bacteria, so deeply situated within the tissues as to be beyond the reach of the antiseptics ; if antiseptics are to be used at all, they must therefore be used in such a strength as (1) to destroy *all* the infected tissue, as when pure carbolic acid is applied to an abscess produced by the *B. anthracis* ; (2) merely to inhibit the multiplication of the bacteria, as when a cavity is irrigated with very weak carbolic acid. The resultant influence of such antiseptic solutions is so slight as to be almost negligible, and they may, as a general rule, be advantageously replaced by the citrate salt solution.

5. The formation of abscesses such as those due to the staphylococcus is often indication of a lowering of the resisting powers of the tissues generally ; this may be due to toxic absorption from the gums (pyorrhœa alveolaris), intestines (constipation or diarrhœa), or elsewhere. Prior attention to these abnormalities is an important essential.

Vaccine Treatment.—In this condition, once the bacterial diagnosis has been established beyond question—and this sometimes may be satisfactorily done by a mere glance at a stained film of the pus—stock vaccines may often be employed with complete satisfaction ; the manufacture of the autogenous vaccine, as a rule, presents so little difficulty that it is to be preferred. The first inoculation may be with a stock vaccine ; if the response be rapid, the preparation of the autogenous vaccine may be

suspended, but if it be not satisfactory subsequent inoculations should consist of the autogenous one.

Dosage.—This will depend somewhat on circumstances : in acute abscesses the initial dosage may advantageously be lower than in the chronic ones. If a primary focus be present elsewhere, the dosage must be adjusted with due regard to the condition there obtaining. The initial dosage in acute infections localized in the superficial tissues alone of the various organisms may be as follows : *Streptococcus*, 25,000,000 ; *pneumococcus*, 25,000,000 ; *B. coli*, *B. typhosus*, *B. pyocyaneus*, 50,000,000 ; *staphylococci*, 100,000,000.

Double these initial dosages may be employed in the case of the more chronic infections, in which the primary infective agent is not these pyogenic cocci, but the *B. tuberculosis*. In such instances tuberculin will almost certainly be essential to cure, and the most suitable preparations are the T.R. and bacillary emulsion, especially the latter : the appropriate initial dose of either is 0.00001 c.c. The initial dosage should not be increased so long as the immunizing response, as judged by the clinical condition, is a satisfactory one ; when increase is necessary, this may be made gradually.

Intervals.—Just as acute infections indicate a small initial dosage, so they indicate repetition at short intervals, reinoculation being advisable when retrogression occurs, provided this is not manifested within twenty-four hours of the inoculation, in which case it may merely indicate a temporary lowering of the resisting power preliminary to a subsequent rise. In acute abscesses experience has shown that repetition may be made at intervals of three to five days ; in chronic conditions, that it may be deferred till the lapse of five to ten days.

Prophylaxis.—When complete recovery has been made, recurrence of the infection may frequently be prevented by the administration of two or three progressive doses of vaccine at intervals of about a week, and at periods of three to six months ; such progressive doses of a staphylococcal vaccine would be 500,000,000, 1,000,000,000, and 2,000,000,000.

Results of Vaccine Treatment.—These will depend largely upon the possibility or otherwise of removing the predisposing factors, such as toxic absorption or the presence of a chronic primary focus elsewhere. When this can be effected, uniformly satisfactory results should be obtained.

ACNE.

Bacteriology.—A slight difference of opinion exists as to the relative ætiological significance of the acne bacillus and the *Staphylococcus albus* in the various conditions grouped together under this name. The probability is that the acne bacillus is present in over 90 per cent. of all cases ; it may be the sole infective agent, and especially is this likely to be the case when comedones alone are present. In about 50 per cent. of all cases the *Staphylococcus albus* is associated with the acne bacillus, and in probably all the cases which present pustulation. Occasionally the staphylococcus appears to be the sole infective agent, and very rarely the *Staphylococcus citreus* or *aureus*, or the streptococcus, may be associated with the acne bacillus. (For an instance of a streptococcal infection, see *Journal of Vaccine Therapy*, vol. i., No. 1, p. 25.) It is thus obvious, if a completely satisfactory result is to be achieved, that a careful bacteriological examination should be made of the secretion, not from one infected focus, but from several, differing the one from the other as much as

possible in clinical characteristics. (For a full account of the bacteriology, see *Journal of Vaccine Therapy*, vol. i., No. 1, p. 23.)

Preliminary Considerations.—1. The situation of the lesions—*i.e.*, in the superficial layers of the sebaceous follicles, sweat glands, or epidermis generally—is such that the ready access of the antibodies is not possible; this is therefore to be encouraged by warm baths, the application of an ethereal soap solution, and free friction of the skin.

2. Reinfection from plugs of sebum, where the bacteria are quite outside the range of attack of antibodies, must be prevented by methodical expression of the plugs; for a similar reason seborrhœa of the scalp must be dealt with by careful brushing, massage, washing, and the application of a suitable pomade, such as the following:

Ung. hydrarg. ammon.	..	..	̄ss.
Ung. hydrarg. rubr.	..	..	̄ss. to ̄i.
Paraffin. molle	..	..	ad ̄i.
Tinct. lavandulæ co.	..	..	q.s.
Misce. Fiat ung.			

3. Acne is almost invariably associated with errors of diet or metabolism, and with the resultant toxic absorption from the bowel; the diet should therefore be adjusted to the peculiarities of the patient, so that regular movement of the bowels is secured; strong saline purgatives should be avoided, but a glass of hot Vichy water on rising and retiring is helpful. If these measures do not suffice, a tablespoonful of pure liquid paraffin after each meal, or a small dose in the morning of a mild saline such as acid sodium phosphate in hot water, will often secure the desired result; occasionally enemata of warm oil or of salt solution are, however, requisite.

If the motions be loose or unduly offensive, or indican be found in the urine, the use of a reliable sour-milk preparation, or of pure cultures of lactic bacilli in malt-extract broth, is indicated.

Plenty of good drinking-water, such as Vittel "Grande Source," will help in elimination of the toxins.

Vaccine Treatment—The Vaccine.—Autogenous vaccines are not always necessary, but if stock vaccines are to prove efficient a careful study of the bacterial infection at several foci should be made. If stock vaccines are employed, they should be polyvalent no less in the case of the acne bacillus than in that of the staphylococcus. If the infection be a double one, the two vaccines may be combined with advantage.

Dosage.—The appropriate initial dosages are : acne bacillus, 5,000,000 ; streptococcus, 25,000,000 ; staphylococcus, 100,000,000. We have already seen that treatment may have to be prolonged and a high ultimate dosage be necessary. So long, however, as the clinical condition is improving under a given dosage, no increase should ever be made. Opsonic index estimations are very seldom required, but a periodic bacteriological examination is often helpful in enabling judgment to be formed as to whether increase in dosage should be made in respect to the *B. acne* or staphylococcus. A change of clinical type from deep indurated foci to small superficial ones which soon pustulate is good indication of progress.

The dosage of *B. acne* vaccine rarely needs to be pushed beyond 25,000,000, but that of the staphylococcus may sometimes ultimately have to reach 2,000,000,000, and very occasionally 4,000,000,000.

Intervals.—Clinical experience has shown that intervals

of seven to eight days are usually suitable ; the best indication for repetition is, however, a slight retrogression occurring after five days. I am sure that too oft repeated administration, especially of the high dosages, militates more against a good result than does too long intervals. Treatment may have to be prolonged for six to twelve months, or even longer.

Results.—The appraisalment of the results obtained by vaccine therapy in cases of acne depends entirely upon what is regarded as *cure*. ‘Absolute’ cure may be regarded as having been secured when no recurrence occurs, say, after the lapse of twelve months ; such cure is only obtained by great attention to detail and the prolonged administration of vaccine. It is, perhaps, obtainable in 50 per cent. of cases, especially if any tendency to relapse is forestalled by a few full prophylactic doses at intervals of six months. Jones (‘Therapeutic Inoculation,’ p. 103) thus summarizes the results obtained in 67 cases at St. Mary’s Hospital : Cured, 12 ; improved, 21 ; slightly improved, 21 ; unchanged, 12 ; worse, 2. These results I should be disposed to call exceedingly unsatisfactory in private practice, but three important factors are concerned therein :

1. The fact that in only eight cases was a higher dosage than 500,000,000 attained.
2. Possible too short duration of treatment.
3. The absolute impossibility of insuring the due observance of the essential preliminaries in the case of hospital patients.

Other observers claim much better results, and a study of their papers shows that fuller dosages were often used ; treatment was conducted for considerable periods, and attention paid to details.

At the same time, the question of what constitutes 'cure' is not usually discussed, and I think it ill-judged ever to give a too-confident prognosis; it is always better to wait and see.

LUDWIG'S ANGINA.

Bacteriology.—Insufficiently studied. Streptococcus found in one case by Sir Almroth Wright.

Preliminary Considerations.—This case so well exemplifies the necessity for full attention being paid to preliminary details that I make no apology for abstracting fully the following description¹: 'The patient, a middle-aged man, had in the first instance developed what was taken for an indolent furuncle in the parotid region. When, after considerable delay, this was incised, no trace of pus was met with, and the tissues were found to be everywhere dry and infiltrated. They remained in this condition, and the wound showed absolutely no disposition to heal. Two weeks later the patient, who up to that time had been taking outdoor exercise, was taken seriously ill, and the brawny swelling, which up to that time had been limited to a patch on the left cheek, spread rapidly round the jaw from one ear to another. A surgeon now carried a series of vertical incisions down into the indurated tissues. Twenty-four hours afterwards the patient had lapsed into a condition of low delirium, and the local conditions showed no sign of improvement. When brought to see him, I could not, even at the bottom of the gaping incisions, find sufficient moisture to fill the loop of a platinum needle. Film preparations obtained by pressing cover-glasses against the sides of the wound showed very abundant streptococci, and only here and

¹ Wright, 'Studies in Immunization,' p. 355.

there a leucocyte. Blood from a vein at the elbow, drawn with the intention of making a culture, clotted instantaneously in the syringe.

‘It was immediately clear that what was most urgently required in this case was, not that further means of antibacterial defence should be furnished to the patient, but that such means of antibacterial defence as were already at his disposal should be brought into application upon the streptococci in the focus of infection. With a blood so viscid and coagulable as was that of this patient, it was inconceivable that any lymph should transude into his tissues. It was to be expected, also, that any transuded lymph would immediately clot.’

‘Influenced by these considerations, I prescribed 60-grain doses of citric acid every three hours. Six hours after the treatment had been begun lymph began to ooze into the wounds, and by next morning all the wounds had begun to bleed. The administration of citric acid was now suspended.

‘A culture of the infecting microbes having now been obtained, the opsonic index of the patient’s blood was determined. This working out at 1·8, and very distinct amelioration having taken place in the patient’s symptoms, I did not think it necessary to resort to inoculation treatment. Nor did afterwards any occasion for immunizing intervention arise, the patient making continuous and rapid progress to complete recovery. There is, I think, a lesson in this case which we shall do well to take to heart in connection with all conditions where the access of lymph to the infected tissues is difficult.’

I would only supplement Sir Almroth Wright’s remarks by observing that vaccine therapy does not consist in the mere inoculation of a vaccine ; such measures as this

for the determination of the access of antibodies are an intimate part and parcel of the procedure, and as truly constitute vaccine treatment as does the actual administration of a vaccine. Walters, Coombe, and Solly¹ treated a case of severe facial carbuncle, complicated by parotitis and Ludwig's angina, on similar lines, supplemented by a vaccine of *Staphylococcus aureus* in 25,000,000 dosages, with a very satisfactory result.

BAZIN'S DISEASE.

Whitfield² has treated two cases of this disease with tuberculin: the one apparently recovered completely; the other, after improving enormously at first, relapsed, and seemed to derive little benefit from further treatment.

BOILS.

Bacteriology.—Boils appear to be due invariably to infection by the staphylococcus, usually the *aureus*, but occasionally the *citreus* or *albus*.

The special form of boil so common in Egypt, and known as 'Nile boil,' has been shown by Archibald³ to be also due to the staphylococcus, usually the *aureus*, occasionally the *albus*, and rarely the *citreus*.

Cultural observations on agar or potato should be made in order to determine the precise variety at work.

Preliminary Considerations.—See Abscess.

Vaccine Treatment—1. *The Vaccine.*—If a stock vaccine be employed, this should be a polyvalent one in which all the varieties of staphylococcus are contained. There are

¹ *Lancet*, July 17, 1909, p. 145.

² *Practitioner*, May, 1908, p. 697.

³ *Journal of Vaccine Therapy*, vol. i., No. 11, p. 299.

no difficulties in preparing the autogenous one, and by this procedure all doubts as to the presence of the proper strain are removed.

2 and 3. *Dosage and Intervals*.—As for abscess, and similarly controlled.

Results.—These are satisfactory so far as the immediate attack is concerned, but recurrences must be guarded against by occasional immunization, best done with a combination of the autogenous and a stock polyvalent vaccine. Archibald has secured most excellent results from this therapy in cases of Nile boil, which are otherwise very refractory to treatment. He follows up the initial dose of 250,000,000 with one of 500,000,000 four days later; then weekly doses of 500,000,000 till six in all have been given, although the condition usually clears up after the third or fourth injection.

CARBUNCLES.

Bacteriology.—The *Staphylococcus aureus* appears to be invariably responsible.

Preliminary Considerations.—One of the most important of these is that carbuncles commonly occur in diabetic subjects; the urine should therefore be tested for sugar, and if this be found, routine treatment for the diabetes should be initiated. As we shall see later, the treatment of diabetes by means of a vaccine of *Staphylococcus aureus* is frequently productive of much good. The removal of sloughs and the application of citrate-salt solution dressings is an important adjunct to vaccine treatment.

Vaccine Treatment.—As for acute abscess due to the staphylococcus; the results are almost uniformly satisfactory. (For six interesting cases in diabetics see Shivdas.¹)

¹ *Journal of Vaccine Therapy*, vol. i., No. 4, p. 100.

CARCINOMA.

Bacteriology.—As carcinoma does not appear to be a bacterial disease, the only connections which it has with bacteriology are—(1) The secondary infections, which may involve an ulcerated surface ; (2) the fact that the *Micrococcus neoformans* of Doyen—which appears to be a variety of staphylococcus—is almost constantly found at the periphery of the tumour, and is accounted to be responsible for some of the pain and cachectic symptoms.

Preliminary Considerations.—Inasmuch as vaccine treatment can only be directed against the secondary infections and to the relief of pain and cachexia, it is well to explain thoroughly to the patient that the disease itself will perforce remain uninfluenced.

Vaccine Treatment.—For that of the secondary infections of ulcerated surfaces, see under Ulcers. A vaccine of the *Micrococcus neoformans* has received a fair trial at the hands of several observers. The consensus of opinion is that it definitely influences the pain and tenderness, the amount of infiltration, and the cachectic symptoms, but that it is without influence otherwise on the course of the disease. Jacobs and Geets¹ hold a rather more favourable view of its influence from their experiences in thirty-seven cases of mammary carcinoma. They tabulated their results as follows :

'Cure' maintained after several months					7 cases.
Lasting improvement	..	..	..	..	12 ..
Transient result	..	..	..	..	7 ..
No result	..	..	..	..	11 ..
Total					37 ..

¹ *Lancet*, April 7, 1906, p. 964.

They state that there is decrease of the surrounding infiltration, reduction in the size of the nodules, which usually become freely movable, great improvement in the patient's appearance and general condition, and diminution of pain, and that operative interference is thereby considerably facilitated.

The appropriate initial dosage is about 25,000,000 ; this may be gradually increased at intervals of seven to fourteen days, until a maximal dose of 500,000,000 is attained.

CELLULITIS.

Bacteriology.—As cellulitis is a secondary manifestation of a primary infected focus elsewhere, which may or may not be discoverable, the nature of the infection will depend on that of the primary focus. It is also sometimes associated with a general septicæmia. The exact determination of the nature of the infective organism should therefore be attempted by observations conducted on material from the primary focus, on transuded lymph obtained from scarification wounds at the spreading margin, and by blood-cultures if the clinical condition indicates. The commonest organism is undoubtedly the streptococcus, and usually this is a *longus* : the staphylococcus, *B. pyocyaneus*, *B. coli*, pneumococcus, fusiform bacillus, and spirochætes may, however, be responsible. The most typical true cellulitis is that known as “erysipelas,” which is due to a *Streptococcus longus* ; this is fully dealt with under that heading.

Preliminary Considerations.—The most important preliminaries are—

1. What is the nature of the primary lesion, if there be one, and does this require surgical attention ?

2. Does a systemic infection coexist ? In which case the treatment will have to be directed against it the more especially.

3. Should an attempt be made to limit the spreading margin by painting the skin all round at a distance of $\frac{1}{2}$ to 1 inch from the margin with collodion or strong tincture of iodine, or by carrying down an incision into the subcutaneous tissues and packing this with some antiseptic ? In regard to this it may be said that the utility of such measures is very doubtful.

4. Is the blood condition unsatisfactory ? Is it too readily coagulable, as in the particular case of cellulitis already fully described (see Ludwig's Angina) ? Or are the antibodies deficient ?

5. In the cellulitis of loose tissues, such as those of the eyelids, considerable congestion may be present, necessitating the application of leeches, and subsequently of warm fomentations.

Vaccine Treatment.—This will depend somewhat on the nature of the primary lesion and the presence or absence of systemic infection ; in the latter alternative the treatment will be that adapted to the septicæmia (see Chapter VIII.). In most cases the treatment will be similar to that already outlined for Ludwig's angina, and about to be described for erysipelas (see p. 152).

As the infection is an acute one, the initial dosage will be low : Streptococcus, 10,000,000 ; pneumococcus, 10,000,000 to 25,000,000 ; *B. coli* or *B. pyocyaneus*, 25,000,000 ; staphylococcus, 50,000,000 to 100,000,000.

Repetition will be, as a rule, necessary in two to three days, sometimes in twenty-four hours. The clinical condition of the patient, the pulse-rate and temperature, condition of the mind, nature of the spreading margin, and

rapidity of extension, will afford, as a rule, sufficient guide to the conduct of immunization, but the aid of serum tests may be invoked. Satisfactory responses in these directions are indicative of correct dosage, slight retrogression in any particular of the need for repetition.

Careful watch must be kept for the formation of pus, and due measures taken for its relief.

For an interesting account of a very severe case of cellulitis, see an article by Morris.¹

A particular variety of cellulitis which frequently proves troublesome when treated on general lines is "mastitis," or cellulitis of the breast.

Benians² has studied this condition in some detail. He finds that the acute condition is commonly set up by the *Staphylococcus aureus*, less often by the *albus* or the streptococcus. A staphylococcal infection is usually set up via the ducts, and so begins as a lobular infection; whereas the streptococcal usually begins through a lesion of the nipple, and so spreads via the lymphatics, involving the interglandular tissues, and not causing an obstruction of the milk by clotting, as does the staphylococcal form. Sometimes the infection is a double one. The withdrawal of any stagnant milk is a very important preliminary, and if this cannot be done owing to the milk having already clotted, the prospect that suppuration may be prevented by vaccine treatment is not so hopeful. When suppuration has already occurred, some assistance is given to surgical measures. A stock vaccine of *Staphylococcus aureus* may be employed in those instances where there is no history or sign of an external lesion of the nipple.

¹ *Journal of Vaccine Therapy*, vol. i., No. 7, p. 195.

² *British Medical Journal*, April 25, 1911, p. 864.

Chronic mastitis may also be due to either the staphylococcus or the streptococcus, or to both. Vaccine treatment is here not so efficacious, owing to the presence of the considerable scar-tissue characteristic of the condition. Thirteen cases in which the average length of suppuration was fourteen weeks were discharged cured in an average of five and a half weeks from the commencement of the vaccine treatment.

ECZEMA (AND PSORIASIS).

Bacteriology.—The ætiological importance of the rôle of bacteria in this condition is by no means definitely determined. As a primary factor, it is probably not considerable, but as secondary invaders bacteria probably play a part of considerable importance. The condition has not been adequately studied from the bacteriological standpoint, but as far as is known the *Staphylococcus albus* or *citreus* is the most common invader.

Preliminary Considerations.—Due attention must be paid to all digestive arrangements and other predisposing causes; until a fuller study has been made of the disease from the standpoint of vaccine therapy, reliance should be placed on the more orthodox procedures, and vaccines employed as, possibly, a useful adjunct.

Vaccine Treatment.—Dosage and intervals as for acne, though possibly shorter intervals may be advantageously employed.

Results.—Miller¹ claims to have obtained some sensational cures, but also admits failures. Shivdas² gives details of three very severe cases in which cure was

¹ *Journal of Vaccine Therapy*, vol. i., No. 3, p. 78.

² *Ibid.*, vol. i., No. 4, p. 99.

brought about by the administration of doses of stock staphylococcal vaccine, ranging from 100,000,000 to 250,000,000, given at intervals of about eight days. McDonald¹ and Whitfield have also secured very satisfactory results, though some failures have been experienced.

ERYSIPELAS.

Bacteriology.—A streptococcus, *longus* in type, appears to be the true cause of this condition, and can always be isolated from scarification fluid obtained at the growing margin.

Preliminary Considerations.—Unimportant.

Vaccine Treatment.—Ross and Johnson² have studied this question in such detail that a short résumé of their paper will give all the necessary information. They treated all the cases of erysipelas—fifty in number—admitted to the Toronto General Hospital during 1908, and compared the results obtained in the nineteen cases admitted in 1907, which were all treated on non-specific lines, with a similar series of nineteen cases treated by vaccine during 1908. They employed a stock polyvalent vaccine sterilized merely by the addition of 0.5 per cent. carbolic acid, the final vaccine containing 0.25 per cent. of antiseptic. They state that if so prepared, the immunizing power is double that of one sterilized by heating to 60° C. for one hour. Inoculations were performed away from the lesion. In the first sixteen cases they estimated the opsonic index before inoculation, and found that in fourteen cases it was between 0.65 and 0.9, in one was 1.1, and in another 1.3. The index is low immedi-

¹ *Journal of the American Medical Association*, 1910, p. 966.

² *Ibid.*, March 6, 1909.

ately after infection, then rises rapidly in favourable cases, and attains a maximum by the third to fifth day, after which it gradually falls with greater or less rapidity.

Ross and Johnson continued the estimations during the progress of thirteen cases, and found that a subsidence in the signs and symptoms was definitely correlated with a rise in index ; in the one case which alone died, the index was 0.6 before inoculation, and could not be raised above 1.1. They found that the temperature fell shortly after a rise of index, which corresponded closely with marked diminution of toxæmia and definite evidence of localization of the inflammation.

Of the fifty cases, eighteen they classified as 'very severe'—*i.e.*, temperature 103° F. or over, tachycardia, mental dulness, or even delirium, and a considerable area of inflammation, with signs of rapid spread ; twenty were 'severe,' and twelve 'mild.' The most striking effects of inoculation were rapid subsidence of toxæmic symptoms, such as mental unrest or delirium and profound malaise ; even those who were 'very severe' almost invariably felt different within twenty-four to thirty-six hours after the first inoculation. Locally there was as a rule some extension of the process, till after a second inoculation on the following day, or even till after the third ; but whatever extension there was was remarkable, in that (1) the colour was brownish-red instead of angry red ; (2) the swelling of the skin was less ; (3) the tenderness over the area of extension was less acute or abolished ; (4) pain was diminished ; (5) the growing margin was rarely raised, but faded off into the adjacent tissues.

The first sixteen cases of the series were treated under the guidance of the opsonic index, but they found that rise of index was so closely correlated with clinical im-

provement that they then abandoned the estimation, and consider they subsequently achieved equally good results.

Dosage and Intervals.—In severe cases initial dosage was 10,000,000 ; in the less severe, 20,000,000. On the second day the severe cases received 10,000,000 if improvement was evidenced by clearing of the intellect and a less intense inflammation. The temperature they did not find a very satisfactory guide, but a fall of 2° to 3° F. they regarded as a valuable indication for reinoculation. If the severe cases showed no improvement, only 5,000,000 were given on the second day. In the less severe cases immediate improvement was almost always shown, and 10,000,000 only were given as the second dose ; 5,000,000, 10,000,000, or 20,000,000 were then given every other day, until a week had elapsed from the establishment of a normal temperature and the disappearance of all erythema. Their rule was, the more severe the case and the less satisfactory the clinical response, the smaller should be the subsequent doses.

Results.—Their results in the two series of nineteen cases may be tabulated thus :

How Treated.	Temperature Normal in 24 Hours.	Temperature Normal in 48 Hours.	Average Dura- tion of Pyrexia in Days	Complica- tion.	Average Duration of Illness in Days.
Non-specific	3	13	8·9	In 6	25·0
Specific	9	5	3·1	In 1	12·8

Death occurred in only one instance, and this was comatose on admission. While they desire carefully to avoid drawing any too strict comparisons, they feel justified in stating that definite advantages are secured in the following directions :

1. Whatever surface becomes subsequently involved, the inflammation is less severe.

2. Mental unrest and physical discomfort are rapidly controlled.

3. The pyrexia subsides more rapidly, and long-continued pyrexia is not encountered.

4. Complications and sequelæ seem much less common. Various other observers have recorded small series of cases, and the results they have obtained are little different from those observed by Ross and Johnson.

FISTULA AND SINUS.

Bacteriology.—In these conditions the *B. tuberculosis* is by far the most common primary invader; it is rare, however, for an infection to be a simple one, secondary infection by one or more of the pyogenic cocci being the rule. The site of the lesion has some influence on the bacteriology: thus, if it be situated on the surface of a limb, the staphylococcus or streptococcus will probably find entrance; if connected with the lung, the streptococcus, pneumococcus or *B. influenzae* will probably be found; if near the intestinal tract, the *B. coli*, *B. proteus*, *B. pyocyaneus*, staphylococcus, or streptococcus may be present. Two or more allied invaders may be associated together. It is thus obvious that a careful detailed examination must be made, and perhaps the aid of 'serum' tests invoked. While the judicious use of vaccines, directed against the secondary infection alone, is likely to be productive of much good, it can hardly be expected to bring about extinction of an underlying infection by the *B. tuberculosis*; this may require the administration of tuberculin.

Preliminary Considerations.—Fistulae and sinuses, from

their great chronicity, are apt to be lined by layers of fibrous tissue impermeable to the lymph; scraping may therefore be very advisable, and irrigation with citrate salt solution necessary. Furthermore, they show a great tendency to close at the exit; this results in the retention of discharge, and is very prejudicial to recovery. Healing must take place from the bottom, and premature or irregular closure be prevented by occasional probing and the insertion, if possible, of fine drains—a wick of gauze may prove efficient.

Vaccine Treatment—Vaccine.—A stock vaccine may yield a satisfactory result, but, in view of the varying nature of the infection and its possible complexity, suitable autogenous ones are much to be preferred.

Dosage and Intervals.—Although the condition is usually a chronic one in which full initial doses are admissible, their use may result in too quick healing at undesirable situations, so that it is better to aim at gradual cure, which is best secured by moderate doses at rather long intervals. Such initial doses are appropriate as :

Streptococcus and pneumococcus	..	10 millions.
<i>B. coli</i> , <i>B. proteus</i> , <i>B. pyocyaneus</i>	..	25 millions.
<i>B. influenzae</i>		50-100 millions.
Staphylococcus		100 millions.
Tuberculin T.R. or B.E.		0·00001-0·00002 c.c.

It should be carefully remembered that sinuses infected by the *B. coli* are especially apt to close prematurely, and that this may occur within twenty-four hours of the administration. A common result of this is the production of a rigor, which is then not a sign, as commonly, of overdosage, but of pus under pressure, as the effect of only too efficient dosage. The pus must be afforded outlet, and care taken to prevent such closures in future

by occasional probing, the institution of drainage, irrigation with citrate salt solution, and by reducing future dosages for a time by one half. In these conditions intervals of ten days between the administration will probably not be overlong.

Results.—Treatment may have to be very prolonged, perhaps for twelve months, and ultimate success will depend largely on the care with which the advent of the antibodies to the focus of infection is determined.

Regular observations of the bacteriological condition are essential, especially in mixed infections, where one of the allied invaders may at any time disappear, and perhaps be replaced by an entirely new organism. Cases such as these tax one's care and skill to the utmost, and serum tests may prove a decided help in times of difficulty.

Carmalt Jones¹ gives the results obtained in 52 cases at St. Mary's Hospital as follows : Cured, 10 ; much better, 19 ; better, 10 ; unchanged, 9 ; doubtful, 4 ; and relapse as occurring in 5 cases. Tubercular ulcer and abscess are included within this category, but I think the results may be taken as fairly representing what is likely to be achieved in hospital practice in sinuses and fistulæ ; in private practice slightly better results may be obtained, but it is scarcely wise to give a too optimistic prognosis.

GANGRENE, DIABETIC.

See Diabetes.

GLANDERS.

Bacteriology.—For this disease the *B. mallei* alone is responsible ; the infection may be a widespread one,

¹ 'Therapeutic Inoculation,' p. 107.

involving the blood-stream, lung, spleen, kidneys, etc., but as the cutaneous manifestations are a prominent feature it may be conveniently considered in this section.

Diagnosis.—This is to be made by means of culture experiments from the blood and local lesions of the slowly growing organism on potato and glycerine agar, and confirmed by means of the production of inflammation of the tunica vaginalis in guinea-pigs inoculated intraperitoneally with the culture, and by means of the agglutination reaction observed macroscopically in sedimentation tubes : normal serum, even in 1 in 5, and certainly in 1 in 10 dilution, fails to give the reaction, while the serum of an infected individual gives a positive result often in dilution of 1 in 100, or even higher. Bernstein and Carling¹ find that the mallein test can safely be applied to man in doses of 10 to 15 minims.

Treatment.—Several cases of this very distressing, but fortunately rare, disease in human beings have now been treated by means of vaccines, with apparently a certain measure of success.

Wright² has given a very full account of a case of chronic glanders in a girl of twenty-two, who appears to have been infected from a glanderous pony ; she was in a very grave condition when treatment was begun with 2,000,000 of the autogenous vaccines. The inoculations were controlled by means of the index, the dosage being finally increased to 5,000,000, and the intervals varying from four to thirteen days ; within three months recovery appeared to be complete, and was permanent six months later.

Eyre³ treated one case with an autogenous vaccine

¹ *British Medical Journal*, February 6, 1909, p. 319.

² 'Studies in Immunization,' pp. 406-409.

³ 'Serums, Vaccines, and Toxins,' p. 340.

with some improvement of the local lesions, but the 'mallein' reaction at the site of infection of the vaccine and the rise of temperature were so marked that the patient soon refused to continue the treatment.

Another case in which vaccine treatment, controlled by indicial estimations, was unfortunately a failure, was that of Dr. J. H. Wells.¹ Small and large doses, short and long intervals alike, failed to bring about adequate immunizing responses and prevent a fatal issue.

Zieler² describes a successful result in a case of chronic glanders of six years' duration, in which other forms of treatment had been tried in vain for years. The disease was very widespread, and particularly unfavourable for treatment, as the mucous membranes were extensively involved. A vaccine was prepared of such a strength that 1 c.c. contained a normal loopful of a forty-eight-hour glycerine-agar culture. An injection was given on each of two consecutive days; then an interval of six to eight days was allowed. Within sixteen to twenty-four hours of an inoculation there was a definite rise of temperature; the site of injection became red, swollen, and tender, while sometimes there was a slight focal reaction. In rather more than a fortnight after specific treatment was begun the ulcerated skin and mucous membrane was completely scarred over. No further development of the disease took place, and two months later the patient was discharged. I can find no record of the subsequent history of this case.

Two or three other cases in which a successful result appeared to follow on vaccine treatment are on record.

¹ See Proceedings of the Royal Society of Medicine, supplement, October, 1910, pp. 42 and 66.

² *Wien. Med. Klin.*, May 2, 1909.

Unfortunately, although the authors are diffident of speaking about 'eure,' and are fully awake as to the possibility of the disease making a subsequent reappearance, the after-history of the cases do not appear to be recorded.

IMPETIGO.

Bacteriology.—MaeWatters¹ says that the *Staphylococcus aureus* is the infective agent in those cases which begin as a scab formation, and the streptococcus in those which begin as a bulla.

Preliminary Considerations.—Strict attention to the digestive tract and general cleanliness, the prevention of reinfection through scratching by covering up the lesions, the removal of scabs by hot fomentations, and the promotion of lymph exudate by applications of citrate salt solution, are essential to a good result.

Treatment is very simple ; an initial 100,000,000 dosage of staphylococcus or 25,000,000 to 50,000,000 streptococcus is appropriate. The advisability of subsequent increase will be indicated by failure to effect speedy cure or maintain improvement of the clinical condition. Intervals of seven to eight days will usually prove suitable. The results should be uniformly successful, but relapse may have to be prevented by an occasional short course of immunization, especially if the improved bodily condition is not maintained.

LEPROSY.

Bacteriology.—That the true infective agent in this disease is the acid-fast lepra bacillus, as seen in stained smears and sections of leprous material, is beyond ques-

¹ *Journal of Vaccine Therapy*, vol. i., No. 3, p. 77.

tion ; but some doubt exists as to whether the cultures isolated by Rost, Currie and Clegg, Bayon, Williams, Twort, Duval, and others, are all identical. The bacillus appears to have strongly pleomorphic characteristics, and to belong to the streptothrix group, though frequently it appears as a diphtheroid organism ; it also loses its acid-fast property with some ease. From the point of view of vaccine treatment the identity of the various cultures is of some importance.

Preliminary Considerations.—Leprosy is a very chronic disease, and remissions and retrogressions are common ; there is thus considerable difficulty in appraising the effect of vaccine treatment, and in determining appropriate dosages and intervals.

Vaccine Treatment.—The first attempt at specific immunization was made by Deycke with a preparation known as *nastin*, and consisting of a neutral fat obtained from acid-fast streptothrices, which Deycke admits were not the lepra organism ; the fat, however, he states to be very closely allied biologically and chemically to that of the lepra and tubercle bacillary sheaths. He claims that by injections of this substance the formation of a powerfully lytic substance for the lepra bacillus is promoted, and that the clinical condition may be materially improved or even cured thereby. His claims, however, are not supported by other observers, and a recent paper by Wise and Minett¹ appears to disprove them completely.

The success which has since attended endeavours to grow the bacillus in artificial cultures has enabled various investigators to try the effect of truly specific vaccine treatment on the course of this disease ; the doubts which

¹ *Journal of Tropical Medicine and Hygiene*, September 2, 1912, p. 259.

exist as to the identity of the cultures from which the various vaccines were prepared makes it difficult to arrive at any definite conclusions.

Curric, Clegg, and Hollman,¹ give as their opinion that—

1. Toxins prepared from *B. lepræ* after the method of Koch's old tuberculin appear to be of little or no value in treatment, and that this also holds for a preparation corresponding to the bacillary emulsion.

2. Ordinary suspended killed cultures cannot be advantageously employed in the treatment of leprosy unless very small doses are used, owing to the slow absorption of the material and its tendency to cause abscesses. They tried dosages of 500,000 in a series of cases for over twelve months.

3. Live cultures, while they have produced no beneficial results in their hands, are deserving of further trial in small doses, so that abscess formation may be avoided.

4. As a serum may be prepared which strongly agglutinates the *B. lepræ*, they are in hopes of preparing one which may prove of benefit.

Sandes² has tried the effect upon four cases of a bacillary emulsion administered in dosages progressing from 10,000,000 to 80,000,000, and at intervals of two to three days; treatment was conducted for periods varying from three to seven months. There was apparently no local or general reaction; estimations of the opsonic index proved of no assistance to the determination of appropriate dosages and intervals, and the treatment was distinctly a failure. He, however, thinks it merits a retrial with suitable modifications.

¹ *Public Health Bulletin*, U.S.A., No. 47, September, 1911.

² *Journal of Tropical Medicine and Hygiene*, March 1, 1912, p. 65.

Rost has treated twenty-two cases with a sterilized six-weeks culture in fish broth of a strain closely resembling Williams's chromogenic streptothrix; the average initial dose was 1 c.c. of this vaccine. In nodular cases only a slight reaction is aimed at, but in anæsthetic cases he considers that higher reactions may with benefit and safety be induced, the reason for this being that in these cases the bacilli are situated in the nerves, and the danger of metastasis is therefore distinctly less than in dealing with nodular masses. He first published the results in a series of twelve cases,¹ and regarded five of these as practically cured, and the other seven as much better. A year later² he gave the after-history of these twelve cases, most of which had continued treatment, and the results obtained in ten others. Of the first series those which were regarded as practically cured are now either entirely so, or show very slight signs of having ever been infected; the other seven have still further improved. They all received no other treatment. Of the new series of ten cases, two have not improved; the other eight have done so to a material degree.

Rost now recommends that as much as 3 c.c. of the vaccine should be given to marked anæsthetic cases. He states that, whereas in these asylum cases the progress is very slow, in some private cases he has obtained more rapid improvement by adopting the salt adjuvant, stopping the consumption of sugar and of fish, and causing erythema of the skin by very hot baths, irritating application, or friction a few hours after the injection of the vaccine.

¹ *Indian Medical Gazette*, July, 1911.

² *Loc. cit.*, July, 1912, p. 257.

LUPUS.

Bacteriology.—The tubercle bacillus is the primary infective agent in all cases, but in nearly 70 per cent. of these secondary infection is superadded by the staphylococcus, streptococcus, diphtheroid or other bacilli, the first of these being present in practically all suppurating cases, the streptococcus in the majority of aggravated cases.

Preliminary Considerations.—The great obstacle to the achievement of satisfactory results from tuberculin therapy in lupus is the difficulty in bringing about the adequate advent of the lymph, laden with antibacterial bodies, to the foci of infection. The concurrent application of some method of increasing the blood-supply, such as that by radiant heat or the Finsen light, is therefore likely to prove highly advantageous ; but even with such adjuvants the results are disappointing. Strict attention should be paid to secondary infections. If syphilis be also present, as is frequently the case, specific remedies for this disease must be employed.

Vaccine Treatment.—The dosage and intervals for vaccines directed against the mixed infections are similar to those used in any ulcerated condition (see Ulcers, p. 169). Tuberculin, if employed according to the principles derived from studies of the index, is used in fairly large doses, the initial dosage of 0.00001 c.c. of bacillary emulsion or T.R. being rapidly raised to 0.0001 c.c., or even higher. Injections may be repeated at routine intervals of seven to ten days. Wright still holds that indical control of dosage and intervals is advisable, but most other observers do not agree with this, and appear to secure at least as good results.

Jones¹ summarizes the results obtained at St. Mary's Hospital in a series of 21 cases thus : Cured, 3 ; much better, 9 ; better, 8 ; unchanged, 1. Relapse occurred in 5 instances.

Treatment may have to be prolonged for a year, or even longer.

It would thus appear that while cure is only to be anticipated in a small percentage of cases conducted on these lines, material improvement may be expected in the majority of instances, provided that a close watch be kept on the secondary infection, and the possibility of reinfection by these be borne in mind. The general opinion would seem to be that dependence should primarily be placed on well-established surgical measures and the application of radium or Finsen light, tuberculin being either a last resort when these fail or a useful adjuvant, especially in those instances where a subnormal index is found at the beginning of treatment.

When the method of treatment adopted is the original method of Koch modified in various ways by various observers, much higher dosages and much shorter intervals are employed. The best plan, possibly, is to use old tuberculin until the necrotic tissues are thrown off, and then to resort to the T.R. or B.E. in order to produce immunity, and endeavour to prevent the subsequent relapse which is so prone to follow on the discontinuation of the old tuberculin. According to this method, the plan is to employ such doses as induce strong focal reactions in the form of marked hyperæmia, considerable resultant exudate of lymph, and the casting-off of the involved tissues. The initial dosage of 0.0001 to 0.001 c.c. is rapidly increased at intervals of one, two, or

¹ D. W. Carmalt Jones, 'Therapeutic Inoculation,' p. 106.

three days, until such a focal reaction, which is accompanied by considerable constitutional disturbance, is produced. This is allowed to subside, and treatment resumed with a dosage one-quarter to one-half of that which produced the desired reaction ; this is then again increased rapidly until the same result is once more obtained, when the same procedure is again followed. In this way the patient may finally become tolerant to a dose of 1 c.c. or more of the original tuberculin. That a certain percentage of cures is effected by this procedure is certain, but there are many failures, and toleration to large doses of tuberculin cannot always be obtained, the severity of the constitutional disturbances precluding the use of doses adequate for the production of a sufficient focal reaction. Much disappointment is also apt to be experienced from the fact that a considerable proportion of the apparently cured cases subsequently relapse. Great difference of opinion still exists as to the value of tuberculin therapy and the best method for its administration in this disease. The correct way to regard it is probably that of a useful adjuvant, and nothing more.

NILE BOIL.

See Boils.

ORIENTAL SORE.

Bacteriology.—This condition has now been definitely shown to be due to infection by the spirochæte known as *Leishmania tropica*.

Row¹ has succeeded in growing the parasite on the Nicolle-Novy-McNeal medium. After seven days' incu-

¹ *British Medical Journal*, March 9, 1912, p. 540.

bation, the culture-fluid containing the *spirochaetes* is collected and sterilized by the addition of glycerine.

Treatment.—0.125 c.c. of the undiluted culture is first given tentatively ; if no response, a double dosage is then employed.

Results.—Three cases were treated in this way ; in two the lesions, both ulcerating and non-ulcerating, healed rapidly and completely in about fifteen days. The former lesions left only a slight depression ; the latter neither cicatrix nor pigmentary deposit.

PEMPHIGUS VEGETANS.

Bacteriology.—This is at present undetermined ; various organisms have been found (For full discussion, see Winfield, *Journal of Cutaneous Diseases*, January-February, 1907 ; and Cronquist, *Arch. für Derm.*, 1911.) From two cases of acute pemphigus in butchers, Bulloch isolated a diplococcus. In one case of fatal pemphigus vegetans I isolated a similar but apparently not identical diplococcus, which closely resembled the pneumococcus both from the blood and clear vesicles. In the turbid bullæ *Staphylococcus aureus* was also present, and from the ulcers which occurred in the mouth late in the disease the *B. pyocyaneus*. (For the full account, see paper by Pernet, *Arch. für Derm. u. Syph.*, Band cx., Heft 3, 1911.)

From another case of acute cellulitis of the arm and breast which threatened to develop this condition¹ I isolated a streptococcus from the blood and cellular tissues, a staphylococcus from the turbid bullæ and cellular tissues, and the *B. pyocyaneus* from ulcers in the mouth and the pus from sinuses in the arm and side.

¹ See Morris, *Journal of Vaccine Therapy*, vol. i., No. 7, p. 195.

Cronquist also obtained the *B. pyocyaneus* from a case of his.

I am inclined to think that in the case under the care of Pernet, James, and myself, the diplococcus was definitely concerned with the production of the disease.

Preliminary Considerations.—These cases appear to be invariably fatal, death occurring from enteritis and profound general toxæmia—the result, probably, of absorption from the areas denuded of epidermis. Vaccine treatment, if it is to prove of any avail, should be applied as early as possible. Extreme care must be taken to prevent secondary infections of the bullæ and subcutaneous tissues, and to diminish toxic absorption from the skin and mouth.¹

Vaccine Treatment has so far proved of no avail in two cases; whether the case described by Dr. Morris would have gone on to pemphigus vegetans cannot, of course, be possibly determined; personally, I feel sure it would, the condition so closely resembling in many particulars that obtaining at one time in the case described by Pernet. In this latter case the administration of the vaccine of the diplococcus in doses varying from 50,000.000 to 200,000.000 seemed at one time likely to turn the scale in favour of the patient. The vaccine of staphylococcus in doses of 25,000.000 to 350,000.000 brought about the complete disappearance of this organism. *Early vaccine treatment* holds out the best prospect of cure in this terrible disease.

PSORIASIS.

See Eczema.

SINUSES.

See Fistula.

¹ See Pernet, *loc. cit.*

SYCOSIS.

Bacteriology is an invasion of the hair follicles of the beard, usually by *Staphylococcus aureus*, occasionally by streptococcus; it is often associated with eczema and boils.

Preliminary Considerations.—Constitutional disturbances must receive attention; hot fomentations should be applied, if necessary, to remove scabs, and thereafter occasional dressings with salt citrate solution. Epilation will sometimes prove necessary.

Vaccine Treatment.—Dosage and intervals as for boils and eczema. Treatment may have to be very prolonged; ultimate cure is obtained in about 50 per cent. of cases, and improvement in about 40 per cent.; results vary with the administrator. Thus, McDonald treated and cured four, while Schamberg treated nine, cured one, and only improved six.

ULCERS.

Bacteriology varies greatly. Some are primarily due to the *B. tuberculosis*, others to the *Spirochaeta pallida*; these may be secondarily infected by almost any pyogenic organism. Others are primarily due to these latter. Special organisms are associated with peculiar forms of ulcer; thus, Vincent's fusiform bacillus appears to be responsible for a common form of ulceration in the lower limbs in the South Sea Islands, while Harold¹ has found a diphtheroid bacillus resembling in many ways the *B. xerosis*, but forming acid in glucose and cane-sugar, commonly occurring in intractable soft chancres. Other diphtheroids commonly occur in ulcerative conditions, especially of the female genitalia.

¹ *Journal of the Royal Army Medical Corps*, September, 1912, p. 269

Treatment.—In tuberculous cases, as for lupus ; in secondary infections, as for similar infections in other cutaneous lesions.

In cases due to *B. fusiformis* anaerobic cultures in broth incubated for three days appear to give good results in dosages varying from 0.5 to 2.0 c.c. Harold¹ has employed vaccines of the diphtheroid bacillus in the phagedenic conditions with considerable success. The vaccine was prepared from agar cultures sterilized by 0.5 per cent. carbolic acid. The initial dose was 15,000,000, increased gradually in some cases to 2,000,000,000, intervals being about four days. Marked local reaction, both at the site of inoculation and of the lesion, was produced. The constitutional disturbance was small.

Herbst and Gatewood² appear to have isolated a specific bacillus from sixteen out of twenty-six cases of soft sore, and to have obtained very marked reactions and good results from the use of a vaccine.

In view of the exceedingly variable nature of the infection in cases of ulceration, the bacteriological examination should be a thorough one, and the use of autogenous vaccines is desirable.

WHITLOW.

Bacteriology.—When the more superficial structures are involved, the *Staphylococcus aureus* or streptococcus appears to be the causal organism. This may also be the case with those involving the bone, but sometimes these appear to be primarily tuberculous. (For such a case, see Whitfield, Proceedings of the Royal Society of Medicine, October, 1910, special Vaccine number, p. 95.)

¹ *Loc. cit.*

² *Journal of the American Medical Association*, January 20, 1912.

Vaccine Treatment.—As for other acute cutaneous lesions by these organisms, the results are almost invariably good. Incision may be necessary, and citrate salt dressings a useful adjuvant.

ACTINOMYCOTIC DISEASE OF THE TISSUES.

Inasmuch as actinomycotic infection of the tissues, whether these be subcutaneous, pulmonary, hepatic, or osseous, results in abscess formation, this disease may conveniently be referred to here. A series of eight cases has been recorded by Kinnicutt and Mitter (*Boston Medical and Surgical Journal*, July 18, 1912, p. 90). Four of these were cervico-facial, two pulmonary, and two abdominal. They isolated the organism, implanted single colonies in broth, then grew these for about ten days, transferred them to a sterile tube and ground them up, added salt solution, and sterilized. They were unable to standardize the vaccine, so contented themselves by beginning treatment with very small doses—viz., 0.1 c.c. of the emulsion. This was repeated every day, increments of 0.05 c.c. being taken until a dosage of 0.75 c.c. was obtained. The two thoracic cases were very advanced, and died, although distinct reactions were obtained. Of the abdominal cases, one recovered and one died with secondary involvement of the lungs, despite making some improvement at first. Of the four cervico-facial cases, three completely recovered, and the other is doing well. They conclude that in superficial infections a vaccine is valuable, but that in the pulmonary forms it is useless. Wynn (*British Medical Journal*, March 7, 1908) has also reported a successful result in a case of pulmonary abscess from the use of inoculations of 0.001 milligramme of dried bacterial substance.

CHAPTER VI

DISEASES OF BONES AND JOINTS

Disease.	Infective Agents.
Acute osteitis, periostitis, and osteomyelitis	<i>B. typhosus</i> , pneumococcus, streptococcus, and staphylococcus.
Chronic osteitis, periostitis, and osteomyelitis	<i>Spirochæta pallida</i> , <i>B. tuberculosis</i> (primary), staphylococcus, streptococcus, <i>B. coli</i> , <i>B. pyocyaneus</i> , bacillus of Friedländer (secondary).
Acute arthritis . .	<i>Streptococcus rheumaticus</i> , gonococcus, pneumococcus, streptococcus, staphylococcus, and pyogenic organisms generally.
Chronic arthritis . .	<i>B. tuberculosis</i> , <i>Streptococcus rheumaticus</i> , gonococcus.
Rheumatoid arthritis	? <i>Streptococcus salivarius</i> .
Villous polyarthritis	? Streptococcus, ? Schüller's bacillus.

ACUTE DISEASE OF BONY STRUCTURES.

This is usually the result of an injury ; occasionally it is a local manifestation of a general infection, or of a chronic one localized elsewhere, as in cases of periostitis due to the *B. typhosus*.

Bacteriology.—The *B. typhosus* or its allies, or any of the pyogenic cocci, may be responsible for the condition.

General treatment must be conducted on well-recognized surgical lines.

Vaccine Treatment, as regards dosage, intervals, etc.,

is very similar to that for similar acute cutaneous lesions. In infections due to the *B. typhosus* an initial dose of 50,000,000 may be employed.

CHRONIC DISEASE OF BONY STRUCTURES.

Preliminary Considerations.—In all diseases of bones and joints the application of general surgical principles, prior to use of vaccines, is essential. No vaccine can be expected to bring about liquefaction and absorption of dead tissues ; bony sequestra must therefore be removed, collections of pus afforded outlet, adequate drainage be established, and measures taken to insure an adequate lymph-supply to the infected parts. Bacterial infections of bones and joints are also so frequently merely secondary manifestations of a primary focus elsewhere that diligent search should always be made for the latter, and active treatment be directed to its cure. Furthermore, they are apt to lead in turn to the involvement of the soft tissues, with consequent formation of abscesses and sinuses. The steering of these cases to a successful issue is therefore a task of no small magnitude, and is only to be achieved in many cases after a most careful clinical and bacteriological examination has determined the precise condition. In mixed infections the possibility of the appearance at any time of fresh invaders from without must also be ever borne in mind.

Bacteriology.—In the great majority of cases the *B. tuberculosis* is the primary infective agent. Wassermann's test in doubtful cases will aid considerably in the exclusion of syphilis. Secondary infections are very common, that by the staphylococcus being the most frequent ; next that by the streptococcus. *B. coli*, pneumococci.

bacillus of Friedländer, *B. pyocyaneus*, diphtheroid and other organisms, may also occur. Careful bacteriological examinations are requisite for the determining of its precise nature.

Treatment—Vaccine.—The most suitable preparation of tuberculin is the bacillary emulsion, and this may with advantage be a mixture in equal parts of that derived from the human and bovine type of bacillus respectively. The vaccine directed against the mixed invaders is best autogenous; but if the bacteriology has been carefully worked out, a stock polyvalent vaccine may be substituted. It may, however, be added that the labour involved in fixing the diagnosis may exceed that of preparing the vaccine.

Dosage.—In the determination of the initial dosage, whether of tuberculin or vaccine, several factors must be taken into consideration, such as—(1) Is treatment to be directed primarily to the cure of the original or secondary focus? (2) What is the clinical nature of any coexistent foci—whether primary, secondary, or tertiary in point of incidence? As a rule, it will have to be adopted according to the requirements of the most acute of the foci. Treatment may be simultaneously carried out with tuberculin and vaccine, but personally I think trial should always first be made of the latter, and tuberculin subsequently alternated with it. In this way confusion is best obviated.

As a rough guide, it may be said that the following dosages will probably be devoid of all danger: Tuberculin, B.E. human, bovine, or mixed, 0.00001 c.c.; streptococcus or pneumococcus, 25,000,000; *B. coli*, *B. pyocyaneus*, 25,000,000 to 50,000,000; bacillus of Friedländer or diphtheroid bacillus, 50,000,000; staphylo-

coccus, 100,000,000 to 250,000,000. The guidance of the clinical and bacteriological conditions will be sufficient indication, as a rule, of the advisability of increased dosage, especially if the tuberculin and vaccine be employed in the way I have recommended. Increase should never be made so long as a reaction, general or at the infected foci, is obtained, or the condition shows steady improvement.

Intervals.—If the vaccine and tuberculin be administered together, the intervals should not be less than ten days; if given separately, intervals of five to seven days are, as a rule, suitable.

Results.—Treatment may have to be very prolonged, and relapse is always likely. Complete cure occurs in only a small percentage of cases, but material improvement in the great majority. As a rule, the younger the patient, the better the prognosis.

ACUTE ARTHRITIS.

Bacteriology.—This condition is set up by the advent into the joint of bacteria, which may either already be resident elsewhere within the body, or may reach the focus from without. In the former case a slight injury may be the determining factor, as when an acute infection of a joint is set up in a weakly child who is recovering from measles or scarlet fever, or in an adult convalescent from typhoid fever or pneumonia. On the other hand, it may be a local manifestation of a more general infection elsewhere, as in the cases of acute rheumatism or gonococcal septicæmia.

If the bacteria come from without, they must gain ingress either by means of a punctured wound or during an

operation. The bacteriological possibilities are therefore numerous. In most cases the true diagnosis can be readily established by examination of the pus obtained by aspiration of the joint. Sometimes, however, no bacteria can be found either by direct or cultural examination of material so obtained. The solution of the problem may then be tentatively arrived at by making careful search for a primary lesion, and by consideration of the general nature of the lesion, and conclusions confirmed by application of such serum tests as agglutination and the opsonic index.

The chief micro-organisms responsible for this condition are—

(a) Arriving from without : *Staphylococcus*, *streptococcus*, *B. coli*, *B. pyocyaneus*.

(b) Arriving from within : *Streptococcus*, *pneumococcus*, *B. typhosus*, and more especially *Streptococcus rheumaticus* and *gonococcus*.

General Considerations.—Except in the case of the *B. typhosus* and *Streptococcus rheumaticus*, pus formation almost invariably occurs, and little good can be anticipated from vaccine treatment without the prior application of surgical principles. The repeated aspiration of the collections of pus may suffice in some instances, but is more than likely to prove a failure. In the few cases with which I have had to deal, free drainage has been immediately established. This, combined with vaccine treatment, has sufficed to preserve freely movable joints.

Vaccine Treatment.—One case in which this procedure was followed I have recorded¹ as occurring in a man aged sixty-three. Six days after the onset of a pneumococcal cold synovitis of the right knee appeared, and was followed two days later by thrombosis of the veins of the

¹ *Lancet*, September 11, 1909, p. 780.

right leg, the limb becoming very swollen and œdematous. Three weeks later there was a condition of dry pleurisy in both chests; the evening temperature was about 102° F., and the pulse 140, weak, and irregular. When I saw the patient he looked exceedingly ill. The right leg, ankle, and knee-joint were swollen and œdematous; the knee-joint was so tense that fluctuation could hardly be obtained. On introducing a large needle into it, pus under great pressure was evidenced, and in this numerous capsulated diplococci were to be seen. These proved to be pneumococci. Blood-cultures also were positive for this organism. A dose of 50,000,000 pneumococci was given, and two days later Mr. Drew operated and found both knee and ankle-joint full of pus, communication between the two being established by a huge abscess burrowing through the muscles of the calf. There was also a large abscess in the thigh communicating with the knee-joint. Free drainage was maintained, and the patient at once began to improve. The vaccine was continued at intervals of about ten days, the dose being doubled after each two or three inoculations, with the result that the patient made a recovery practically complete within two months.

A sufficient number of similar cases have now been recorded¹ to show that vaccine treatment is a most valuable adjuvant to surgical measures in this serious condition, in that it produces a speedy and marked improvement in the general condition, hastens convalescence, and assists materially in the maintenance of a movable joint.

Small dosages and short intervals are to be preferred. The clinical condition, general and local, and the pulse and temperature, are as a rule sufficient guides.

¹ For one, due to *B. pyocyaneus*, see Groves, *British Medical Journal*, May 15, 1909, p. 1169.

Such initial dosages as streptococcus 10,000,000, pneumococcus 10,000,000 to 25,000,000, *B. coli*, *B. pyocyaneus* 25,000,000, staphylococcus 50,000,000 to 100,000,000, may be safely employed, and repeated or increased according to indications at intervals of three to five days.

Infections by the *B. typhosus* may be, perhaps, safely dealt with by fixation of the limb in a good position, aspiration, and a vaccine in doses of 25,000,000 to 50,000,000. I can, however, find no record of a case in which vaccine treatment has been utilized.

Arthritis, acute and chronic, due to the *Streptococcus rheumaticus* (see Rheumatic Fever).

ARTHRITIS, ACUTE AND CHRONIC, DUE TO THE GONOCOCCUS, is set up by the dissemination through the bloodstream of the organisms resident in the urethra, prostate, seminal vesicles, or other focus. It is therefore obvious that, if the arthritic condition is to be adequately dealt with, attention must also be directed to the appropriate treatment of the primary focus of infection; and, while it is quite true that vaccine treatment directed against the arthritic condition alone may often suffice for the simultaneous cure of the primary focus, no reliance should be placed on this contingency, but every effort should be made to deal with the primary cause of all the trouble in a satisfactory manner. This holds with especial force in regard to the chronic form of this disease, and it is to omissions in this direction that many of the failures ascribed to vaccine treatment are due. As I have already said, vaccine treatment does not consist in merely administering certain doses of vaccine at certain intervals, but in the addition of this therapeutic measure to all such other procedures as are to the advantage of the

patient. In chronic gonococcal arthritis, a condition of chronic urethritis very often coexists. The gonococci at the former focus may be within striking distance of the vaccine, but those at the latter focus may be so encapsulated within the crypts and sinuses as to be entirely outside the reach of the antibodies, unless methodical dilatation of the urethra and other measures are employed. It thus follows that, while vaccine alone may apparently bring about an immediate cure, subsequent setting free of the bacteria enshrined at the primary focus may at any time determine a fresh infection of the joints. An acute arthritis coming on during the second or third week of a first attack of gonorrhœa is therefore much more responsive to treatment than is one which appears during the subacute stage of a second or third attack, or in the course of a chronic urethritis.

Diagnosis.—In the *acute* forms the correct diagnosis may as a rule be inferred from the presence of a primary lesion due to gonococcus elsewhere, and from the nature of the joints affected. This may be substantiated by examination of some puncture fluid and by indicial estimations.

In the subacute and chronic forms considerably greater difficulty may be experienced. A provisional diagnosis may then be confirmed—(1) By examination of puncture fluid ; (2) by determination of the index ; (3) by making diagnostic use of a vaccine. This procedure has been much employed in America, and I have at times found it of the greatest service. It is conducted as follows : The patient is put to bed, and the temperature taken at intervals of two to four hours for thirty-six to forty-eight hours. A dose of 500,000,000 gonococci is then administered subcutaneously, and the temperature observations

continued, the clinical condition being also noted. If the gonococcus be not the infective agent, a slight rise of temperature, perhaps 0.5° F., may be noticed; but there is no marked rise, no general malaise, headache, or increase of pain, tenderness, or redness of the joints. On the other hand, a rise of temperature of 1.5° to 2.0° F., headache and general malaise, and increased pain, tenderness, and redness of the affected joints, is pathognomonic of gonococcal infection. The particulars of two recent cases in which I have thus been enabled to make the correct diagnosis, as adjudged by the results of vaccine treatment, are as follows: The first was the case of a doctor, stationed in Nigeria; he had had gonorrhœa some years ago, which appeared to have cleared up completely. Between two and three years ago he began to have pain and swelling in various joints, and various forms of treatment were of no avail. He was seen by various specialists, who were not sure of the precise nature of the infection, especially as advanced pyorrhœa alveolaris was present. I advised him to try a diagnostic dose of gonococcal vaccine. At 1.30 a.m., when his temperature was 98.9° F. and pulse 68, he injected 500,000,000. The following is his account of the reaction:

Time.	Temperature. ° F.	Pulse.	Remarks.
1.30 a.m.	98.9	68	Injection.
6 a.m.	98.2	64	
12 noon	100.3	78	Before this some shivering.
2 p.m.	100.9	92	
5 p.m.	101.0	96	
8 p.m.	98.6	92	
11 p.m.	99.2	80	

‘During the whole day there was general malaise, but no increase of joint pains. By next day the pyrexia had quite subsided, but there was general malaise and decided pain and weakness of the joints. During the next few days there was decided improvement in all the joints. I can now walk without limping, and can make good use of practically all my joints, though some weakness is still present in them, and I can elicit pain by certain movements.’ The patient returned to Africa, and continued the treatment, with very good results.

CHART I .



The second case was that of a young man who had had a first and only attack of gonorrhœa a few years ago. He came of a gouty stock. He was put to bed for twenty-four hours, and his temperature taken four-hourly. At 10 a.m. an injection of 500,000,000 gonococci was administered; the effect is to be seen in Chart No. IX. At 9 p.m. a rigor began, and at 10 p.m. the temperature rose to 102.8° F. He had considerable headache, and felt very out of sorts; there was also increased pain and tenderness of the affected joints. Twenty-four hours

after the inoculation the temperature began to fall rapidly, and the following day the patient was walking about again, the local condition having materially improved on what it was prior to the inoculation.

I have never seen the slightest ill-effect result from this procedure, which may be similarly applied in doubtful infections by the *Streptococcus rheumaticus* (diagnostic dose, 100,000,000), or in those by the streptococcus of the mouth in cases where marked pyorrhœa alveolaris is also present (diagnostic dose, 250,000,000 to 500,000,000).

Vaccine Treatment.—In acute gonococcal arthritis the arthritic condition is the most important one clinically, unless a septicæmic invasion be present or a condition of acute prostatitis. In either case an initial dosage of 10,000,000 is probably quite devoid of danger. This may be repeated or increased at intervals of two to four days, according to the clinical signs and symptoms. The control of the opsonic index I do not think necessary nor even helpful, in view of the rapid changes which are almost certainly taking place in its value.

In chronic gonococcal arthritis the index is nearly always persistently subnormal, and its estimation may give a very fair idea of the progress of immunity; but here also clinical signs and symptoms are sufficient guide.

Cole and Meakins¹ have recorded their experiences with vaccines in fifteen cases, Irons² in thirty-one cases. Hartwell³ in fifty-one cases, and MacDonald⁴ in fourteen cases. All agree in concluding that the treatment is of

¹ *Bulletin of Johns Hopkins Hospital*, June and July, 1907, p. 223.

² *Archives of Internal Medicine*, vol. i., No. 4, p. 433.

³ *Annals of Surgery*, 1909, p. 939.

⁴ *Journal of the American Medical Association*, 1910, p. 966.

distinct value, materially shortening the duration of the infection in all stages. Hartwell found that the best results were obtained in the more chronic cases, and that in the early ones it did not seem capable of preventing extension to fresh joints, nor of producing sufficient lasting immunity to prevent recurrence. This may have been due to two causes—(1) Insufficient attention having been paid to primary foci; (2) inadequate final dosage and an incomplete course of treatment. All are very cautious in drawing too definite conclusions, recognizing the great variations which may spontaneously occur in the course of this disease. Irons, like Hartwell, saw the best results in subacute and chronic cases, although in several acute cases improvement appeared to follow rapidly on an injection.

They tabulate their results as follows :

Observer.			Cases.	Cured.	Benefited.	Not Benefited.
Irons	..	..	31	18	9	4
Hartwell	..	..	51	?	42	9
MacDonald	..	..	14	9	1	4

The initial dosages and intervals employed varied with the observers. Thus Cole and Meakins began with 200,000,000 to 300,000,000, and employed intervals of seven to ten days; Irons with 20,000,000 to 50,000,000, and his intervals were three to seven days; Hartwell with 10,000,000 to 25,000,000, and employed intervals of two to four days.

The rather unsatisfactory nature of the results obtained at St. Mary's Hospital¹ is, I think, due entirely to

¹ Jones, 'Therapeutic Inoculation,' p. 131.

the inadequate pushing of the dosage; 50,000,000 was never exceeded. Of twenty-three cases, three are described as cured, seven as much better, and thirteen as better.

Generally, it may be stated that both initial dosages and intervals must depend on the severity of the most severe clinical condition present, and on the responses made to the inoculations. In acute cases 10,000,000 may be used to begin with, the intervals being two to five days; in subacute cases the initial dose may be raised to 25,000,000, and the interval be three to seven days; in chronic cases the dosage may be 50,000,000 to 100,000,000, and the intervals five to ten days. Treatment should be prolonged for several weeks after either complete recovery has been secured or the patient fails to make further progress. In both subacute and chronic cases the ultimate dosage should not be less than 500,000,000. Polyvalent heterogeneous vaccine appears to give quite as good results as autogenous ones.

CHRONIC ARTHRITIS DUE TO THE 'B. TUBERCULOSIS.'

The fullest account of the use of vaccines in this disease is given in the excellent analysis by Maynard Smith¹ of the results obtained in thirty-four cases treated at St. Mary's Hospital.

Preliminary Considerations.—See under Chronic Diseases of Bony Structures. Regard should especially be paid to the question of mixed infection, and to the application of general surgical principles.

¹ *British Medical Journal*, 1909, vol. ii., p. 1047; Proceedings of the Royal Society of Medicine, vol. iii., No. 9, Supplement, p. 128.

Vaccine Treatment.—This is usually carried out with T.R. or B.E., the initial dosage of 0·00001 c.c. being gradually increased at intervals of seven to ten days, until a final dosage of 0·0002 to 0·0005 c.c. has been attained. As in this method of treatment generally, it is unwise ever to increase the dosage so long as an immunizing response is being obtained. Clinical signs and symptoms are usually a sufficient guide, but opsonic index determinations are employed by some (as in the St. Mary's Hospital series). Index observations are especially useful to determine whether cure is finally complete, evidence being sought of the inability to induce auto-inoculations by massage, passive or active movement. The treatment of mixed infections is to be conducted on the lines laid down in the preceding chapter.

The results of vaccine treatment as observed in the above series of thirty-four cases are set out in the following abstract. Three only of the thirty-four cases were treated by inoculation from the beginning; all the other cases had been treated by other methods before they came to the Inoculation Department. Of these three cases, two were cured, with complete restoration of function; by this is meant that an observer who did not know the case could not tell which had been the diseased joint. The third was cured, but there was some deformity and limitation of movement remaining. Of the other thirty-one cases, sixteen had been under treatment by splinting, rest, and in some cases operations, during twelve months or less before they came under inoculation treatment. In ten a cure ensued, with complete and absolute restoration of function, so that no one could

tell by clinical observation which had been the joint affected ; two were cured with slight limitation of movement ; four were improved, but were still under treatment. The remaining fifteen cases had already undergone more than twelve months' treatment by splinting, rest, open air, and operation ; of these, two had only been under treatment for a couple of months at the time of this report, one had been treated for six months and one for ten months without improvement. Of the remaining eleven, six were cured, five were improved and still under treatment. As these were all hospital out-patients, complete rest was often impossible, and such advantages as are afforded by seaside convalescent homes were not available.'

Maynard Smith concludes that these are better results than he himself has been able to obtain by other methods without the aid of vaccine treatment. Consideration of the series of fifteen cases which had already undergone more than twelve months' treatment on more orthodox lines may fairly lead to the conclusion that the simultaneous use of tuberculin will give better results than are obtainable by purely surgical methods. In cases where mixed infections are present vaccine treatment directed against these invaders may be absolutely essential for a cure. These cases are, however, much the most difficult, and prolonged treatment may be necessary. In several of which I have had care complete cure has not been attained even in twelve to twenty-four months ; but what has been achieved has been this : that, whereas formerly the sinuses were discharging several ounces of pus per day, now they are nearly dry, and there has been a corresponding improvement in the comfort and general condition of the patient.

The results obtained by various observers may be tabulated thus :

Observer.	Number of Cases.	Cured.	Improved.	Not Improved.
Maynard Smith ..	34	11	19	3
Western ..	26	14	7	5
McArthurs ..	19	1	15	3
Thomas ..	20	0	15	5

For the divergent results obtained by the former two and later two observers it is somewhat difficult to find an explanation; possibly the stage of the cases, the duration of treatment, and an exigent standard for cure, may not have been without influence.

It may be given as a general rule that in young subjects and early cases cure and good movement can be expected, but where there is much destruction of tissues and sinuses are present, progress is slow and movement may be considerably limited.

Chronic arthritis due to the *Streptococcus rheumaticus* (see Rheumatic Fever).

Chronic arthritis due to the gonococcus (see under Acute Arthritis).

RHEUMATOID ARTHRITIS.

Preliminary Considerations.—Many endeavours have been made to obtain some organism from the affected parts which might be regarded as a specific cause of the condition. Although in the majority of instances no organism has been obtained either in smear or culture preparations, at times some organism or other has been isolated.

The sterility of the fluid in most cases had led to the opinion being advanced that in those instances where bacteria have been found they have been nothing more than chance invaders. The organism most commonly found has been a short streptococcus, which appears to be capable of initiating arthritic changes when introduced into the joints of animals. In one case of subacute polyarthritis, in which great care was taken to exclude chance infection, I not only obtained this organism, but also cultures of a spirochæte, which had the appearance of two vibrios placed end to end. On blood-agar this organism formed round, heaped-up, glutinous colonies, just like drops of yellow honey. Animal inoculation experiments, unfortunately, could not be made. The most popular view is that this condition—or, rather, group of conditions, for here I am including all cases of subacute and chronic polyarthritis of which the specific infective agent is unknown—is due to the action of certain bacteria or their toxins, the bacteria not necessarily being located in the joints, but in some distant focus, such as the gums, the intestines, or the kidneys. It has thus come about that search has been made for some more or less specific organism at one or other of these foci. Recent investigations have shown that the frequency with which bacteria gain entry into the general circulation, especially from the whole alimentary tract, has been in the past greatly underestimated. Careful blood-cultures taken in cases of subacute polyarthritis have yielded positive results in a considerable percentage of cases, the bacterium most commonly found being a streptococcus, sometimes of the *salivarius* (i.e., mouth) type, sometimes of the *fæcalis* (i.e., intestinal) type, sometimes of a more or less aberrant type. The view,

therefore, that the primary focus of infection may be resident in the gums or intestines, and that bacteria, and especially streptococci, may reach the blood-stream therefrom and be carried to the joints, where they may at times be found, is not altogether devoid of experimental confirmation. While it is perfectly true that infection of the gums by a streptococcus (*i.e.*, pyorrhœa alveolaris) is exceedingly common, yet rheumatoid arthritis is relatively rare, it is equally true that there are very few cases of rheumatoid arthritis in which advanced pyorrhœa alveolaris is not present. So also the *B. coli* is present in all human intestines, yet only occasionally does it set up an appendicitis or enteritis. If this view of the ætiology of these forms of arthritis be correct, it necessarily follows that diligent search must be made for some primary focus of disease, whether in the gums, tonsils, intestines, urethra, vagina, or uterus; that serum tests should be made with such bacteria as are isolated in an endeavour to learn whether they are really exerting any pathological function, and that active measures should be taken to obtain extinction of any such primary focus.

Vaccine Treatment.—This, except in those few instances where bacteria are obtained from the infected joints, must be conducted on more or less empirical lines. As we shall see, results tend to justify this procedure. In many cases, my own included, where bacteria have been isolated, very modified success has attended vaccine treatment, possibly because in these cases less attention is directed towards some possibly primary focus, but see also p. 288.

Jones¹ records two cases which were treated at St. Mary's Hospital with the vaccine of an organism ob-

¹ *Loc. cit.*, p. 133.

tained from the urine, which in characteristics was intermediate between a streptococcus and a staphylococcus. Considerable relief of the arthritis is said to have been produced. It may be mentioned that streptococci of various types can frequently be obtained from the urine, not only of cases with arthritis, but also of apparently healthy individuals.

Bannatyne and Lindsay¹ obtained from the blood of two patients with advanced rheumatoid arthritis an organism which also seems, from a somewhat imperfect description, to have been intermediate between a staphylococcus and a streptococcus (or pneumococcus). They obtained excellent results from the use of the vaccine in doses of 5,000,000 every two or three days.

Charlton Briscoe,² after rightly insisting on the prime necessity of searching for and treating any primary focus of bacterial infection, considers that vaccine treatment holds out definite hopes of amelioration.

The primary focus to which the greatest attention has been paid is that of the gums affected by the condition known as pyorrhœa alveolaris. As we shall see (p. 195), the bacteriology of this condition is a very complex one, but one organism commonly present has been singled out for special attention. This streptococcus—or, as Goadby prefers to call it, a 'strepto-bacillus'—is fully described in the *Lancet* for March 11, 1911. The injection of this bacillus—which is present in the pus of practically every case of pyorrhœa alveolaris—into the joints of rabbits produces a condition indistinguishable from that of arthritis deformans; but inasmuch as rabbits are very subject to arthritic changes, and as these can

¹ *British Medical Journal*, January 28, 1911, p. 192.

² *Ibid.*, March 11, 1911, p. 545.

be induced by inoculation with various other non-pyogenic organisms, this evidence does not afford any very strong confirmation of its influence in the production of arthritic changes in man. The therapeutic use of the corresponding vaccines by numerous observers has, however, produced such effects that the pathological significance of this streptococcus of the mouth cannot be disregarded. Goadby¹ gives the results he has obtained by the use of this vaccine in a series of twenty-two cases in which definite arthritis of one or more joints accompanied a septic condition of the gums, this latter also receiving local treatment :

Number of cases	..	..	..	22
Cured	..	..	..	12
Improved	..	..	..	6
No improvement	..	..	..	4

The number of cases in which cure or definite improvement of the arthritic condition was brought about by these means strongly indicates that there is a definite connection between the organisms of pyorrhœa alveolaris in general and of the streptococcus in particular and arthritic changes.

The initial dose of the vaccine is 10,000,000, and the intervals five to seven days. The dosage may require raising ultimately to 250,000,000 to 500,000,000, and treatment may have to be prolonged over six to twelve months.

Numerous other workers have achieved results similar to those of Goadby's, and it would appear that definite hopes, at least of considerable improvement, can be formed in a very large percentage of cases, provided that strict attention can be paid to the primary foci.

¹ *Loc. cit.*

Veitch has given an exceedingly interesting account of the results achieved in a large series of cases in which strict attention to primary foci was combined with vaccine treatment.¹ His methods and results are described in the section devoted to acute rheumatism and its complications (see p. 288).

VILLOUS POLYARTHRITIS.

A specific micro-organism for this affection has been described by Schüller,² and by Fayerweather.³

Painter⁴ treated six cases with a vaccine compounded of streptococcus and Schüller's bacillus ; the results were quite negative.

¹ *Journal of Vaccine Therapy*, vol. i., No. 10, p. 269.

² *Berliner Klin. Woch.*, September 4, 1893.

³ *American Journal of Medical Science*, December, 1905.

⁴ *Boston Medical and Surgical Journal*, 1907, p. 621.

CHAPTER VII

DISEASES OF THE DIGESTIVE TRACT

Disease of—	Infective Agents.
The gums	Streptococcus, pneumococcus, <i>M. catarrhalis</i> , staphylococcus, spirochætes, vibrios, etc.
Tonsils	As of the gums ; also <i>B. tuberculosis</i> .
Salivary glands ..	Streptococcus, pneumococcus, staphylococcus.
Stomach	Streptococcus, pneumococcus, <i>B. coli</i> , <i>B. tuberculosis</i> .
Duodenum	As of the stomach.
Liver and gall-bladder	Streptococcus, <i>B. coli</i> , <i>B. typhosus</i> .
Pancreas	Staphylococcus, streptococcus, <i>B. coli</i> .
Small intestine ..	<i>B. typhosus</i> and its allies, <i>B. coli</i> and its allies, <i>Vibrio cholerae</i> , streptococcus, <i>B. acidi lactici</i> , <i>B. tuberculosis</i> .
Large intestine and appendix	<i>B. coli</i> , <i>B. dysenteriae</i> , streptococcus, <i>B. acidi lactici</i> , <i>B. tuberculosis</i> .
Rectum	Pyogenic organisms generally, especially streptococcus and staphylococcus.
Peritoneum (acute)	<i>B. coli</i> , pneumococcus, streptococcus, staphylococcus, <i>B. pyocyaneus</i> .
Peritoneum (chronic)	<i>B. tuberculosis</i> .

DISEASE OF THE GUMS.

The infective condition of the gums which is of paramount importance is that known as pyorrhœa alveolaris. We have already seen that there is probably an intimate connection between this disease and certain forms of

arthritis; its connection with follicular tonsillitis, post-nasal catarrh, the various bacterial diseases of the pulmonary tissues, gastritis, enteritis, and anæmia, simple and pernicious, is no less definite. It is thus a disease of very great importance, and deserving of fuller consideration than can be here devoted to it. (For a fuller discussion of this question, see Allen's 'Bacterial Diseases of Respiration and Vaccines in their Treatment.' H. K. Lewis.)

Preliminary Considerations.—In its earliest stages the only obvious evidence of its presence is a slight hyperæmia of the gum margins, and interdental papillæ; in its most advanced forms the teeth are embedded in a pocket of pus; they are loose, tender, and painful, the gum tissues and periosteum are destroyed, and the bony tissues are undergoing a rarefying osteitis. Between these two extremes all possible variations may be found. It is a disease which may begin very early in life. The soft nature of the food now eaten by civilized man fails to keep the teeth clean. Tartar is deposited, and neglect of suitable methods of oral hygiene enable bacteria to gain an easy and undisturbed footing. It is thus obvious that before thought should even be taken of vaccine treatment, the mouth should receive strict attention at the hands of a competent dentist, who has time to devote to the tedious procedures of scaling and polishing the teeth, and of swabbing out all infected pockets with appropriate antiseptics. In advanced cases this will require repeating over and over again, while the patient does his part by daily massaging the gums and rubbing in of eau-de-Cologne, and by carefully cleansing the teeth and gums with suitable brushes and an antiseptic mouth-wash, but not a powder. If the disease be not too far

advanced, the dentist may succeed in completely removing bacterial débris, and the tissues of the gums may closely reapproximate to the teeth. In more advanced cases this may prove to be impossible, and nothing remains but extraction of the teeth. Vaccine treatment is a useful adjuvant to thorough dental treatment. It may aid in the extinction of the bacteria actually inside the tissues of the gums, but it can never have any effect upon those which are lying outside the tissues in the interval between the gum and teeth. As we have already seen, the activities of the bacteria are not confined to the tissues locally ; they have been found on many occasions in the blood-stream, and sometimes appear in the urine. On such wandering bacteria a powerful influence can be brought to bear by means of a vaccine ; but if vaccine treatment is to be used and not abused, its limitations in this disease must be clearly realized.

Bacteriology.—This may be relatively simple or exceedingly complex. In the earliest stages it is possible that one organism only is at work, this being probably a streptococcus, possibly a staphylococcus, or pneumococcus. As the disease progresses, the infection usually becomes a mixed one, the *M. catarrhalis* being commonly added to the ranks of the original invader. Later still it becomes more and more complex, streptococcus, staphylococcus, pneumococcus, and *M. catarrhalis* being present in any combination, and various micrococci and diphtheroid bacilli being superadded. The vibrios, streptothrices, and spirilla of the mouth combine with these, and may finally oust them almost altogether from the stagnant pockets and more superficial parts of the tissues, the original invaders retreating into the deeper parts of the tissues. No attempt, therefore, should ever be

made to determine the bacteriology from the point of view of vaccine treatment until the dentist has cleaned out all the pockets and destroyed the more superficial bacteria. When this has been completed, a little secretion may be taken up from the bottom of a pocket by means of a fine capillary pipette, and a small scraping obtained from the tissues lining it. Smears should be suitably stained and cultures prepared in blood-agar from this material.

Vaccine Treatment.—If desired, index determinations for such bacteria as have been thus isolated may be made, and vaccines prepared from those to which the immunity appears unduly low. Confirmation of the significance of the suspected varieties may be sought by making further estimations after auto-inoculations have been induced by massage of the gums with the finger-tip. If only one or two varieties are isolated, this is hardly necessary, and a combined vaccine may be utilized. As initial dosages, 10,000,000 streptococci or pneumococci, 25,000,000 *M. catarrhalis*, and 50,000,000 to 100,000,000 staphylococci appear to be suitable. The signs of an adequate immunizing response are the production within twenty-four hours of slight malaise or headache, increased tenderness and redness of the gums, and slight increase of any constitutional symptoms, such as joint and muscle pains. These should all pass off within twelve to twenty-four hours. So long as any of these, or an improvement in the local condition, be secured, the dosage should not be increased. A suitable interval between inoculations is one of five to seven days.

Some observers attach such special ætiological significance to the streptococcus that they employ a vaccine of this organism in all cases. This I cannot regard as a very scientific procedure, although it must be admitted

that the streptococcus appears to be the chief infective agent in at least 80 per cent. of all cases.

Results.—The results that are to be expected from a course of vaccine treatment depend on several factors : (1) The stage of the disease ; (2) the skill and care which the dentist simultaneously devotes to the case ; (3) the attention which the patient bestows on himself ; (4) the length of time available for treatment. It also becomes necessary to decide in our own minds what constitutes ‘cure.’ Inasmuch as the causal organisms are always present in the mouth, unlimited opportunities exist for reinfection, and this will inevitably occur unless the pre-existing conditions are obviated. In the earliest stages it is possible by dental and other methods to restore the gums to full health and vitality in the great majority of cases, perhaps in almost every case ; but this condition will only be maintained by great care on the part of the patient, and occasional supervision by the dentist. Accumulations of tartar and of food débris must be prevented and the gums massaged daily.

In all other stages—*i.e.*, when once the gum has begun to lose its intimate connection with the teeth—reinfection is bound to occur sooner or later, unless extreme attention is paid to oral hygiene ; in fact, it might almost be said ‘once a pyorrhœic always a pyorrhœic.’ It is this liability to reinfection that makes it so difficult to decide what constitutes ‘cure.’ It seems fair to agree that this term shall be applied when, six months after the cessation of treatment, (1) the teeth are quite firm in their sockets ; (2) careful pressure reveals no pus and the probe no pockets between the gums and teeth ; (3) the gum tissues are firm and healthy-looking ; (4) there has been no further destruction of

tissue, either of the gum or bony structures ; (5) constitutional and general symptoms have not recurred.

It is only by the earnest combined efforts of dentist, patient, and physician that such results are obtainable, and it should be impossible to speak of the results of inoculation treatment alone, for no physician should allow himself to be persuaded so to neglect the principles of vaccine treatment as to rely on the use of inoculations only. It is the combined attack only which fulfils the requirements of vaccine treatment, and by its due delivery 'cure,' as defined above, should be obtainable in every case that is seen in the earliest stages, in the great majority of instances where the teeth are still firm and the bony structures as yet intact, even when constitutional symptoms are marked ; but when the gums are spongy and destroyed to any great extent, the teeth loose, and the alveolar tissues eroded, amelioration alone is to be expected, and the maintenance of this will depend on constant supervision.

DISEASES OF THE TONSILS.

The diseases of the tonsils in which vaccine treatment may be advantageously employed, are—(1) Tuberculous tonsillitis ; (2) acute tonsillitis and acute peritonsillitis or 'quinsy' ; (3) follicular tonsillitis.

For *tuberculous tonsillitis*, see *Tuberculous Laryngitis*.

Acute Tonsillitis or Peritonsillitis.

Acute tonsillitis is frequently seen in the course of such diseases as diphtheria, scarlet fever, measles, and acute rheumatism. It may also occur independently of such specific diseases.

Bacteriology.—Tonsillitis, occurring independently of the specific infections, is usually due to the streptococcus, staphylococcus, or *M. catarrhalis*, and these organisms are usually found associated with the *B. diphtheriæ* in the diphtheritic form. In scarlet fever a special form of the streptococcus, known as *S. conglomeratus*, is found, usually associated with other forms. In measles it is usually due to a streptococcus, sometimes a staphylococcus, and in acute rheumatism the special form known as *Streptococcus rheumaticus* is primarily responsible; but infection by other forms of the streptococcus is also probably superadded. Owing to the fact that secondary infections by various mouth organisms are almost inevitable when the more superficial parts of the tonsil are involved, the determination of the true infective agent, or agents, is often no easy matter; but when collections of pus occur more deeply in the tissues, this difficulty is seldom encountered, and fortunately it is only in conditions such as these that help is likely to be required from inoculation treatment.

Vaccine Treatment has been little employed in these affections. There would, however, seem considerable scope for its use in acute peritonsillitis or quinsy. For this condition the *Staphylococcus aureus* or streptococcus appears to be responsible. In the earlier stages the infective agent may be determined with reasonable certainty by observations on material taken from the surface of the tonsil, or on material taken by pushing a capillary pipette, in which there are a few drops of broth, some little distance into the swollen tissues, expelling the broth, and then re-aspirating it into the pipette. When pus has formed, ample material for examination is available. When the infective agent has

been determined, a small dose of the appropriate stock vaccine may be at once administered, and the preparation of the autogenous vaccine proceeded with. When this is ready, another dose (10,000,000 to 25,000,000 streptococci, 100,000,000 staphylococci) may be given, and repeated if required at intervals of three to five days. As quinsy has a great tendency to recur, there is a decided advantage in having a supply of the patient's own vaccine, for it may be confidently anticipated that its use at the first signs of recurrence will abort the attack and prevent pus formation.

Follicular Tonsillitis.

Bacteriology.—The bacteriology of this condition is identical with that of pyorrhœa alveolaris.

Preliminary Considerations.—Just as pyorrhœa alveolaris is primarily a matter for the dentist, so this condition is primarily one for the surgeon. The secreting follicles should be extirpated, if they are accessible, or ablation of the tonsil considered. Local applications of chinosol, (1 part), glycerine (200 to 500 parts), are often very helpful.

This condition frequently coexists with that of pyorrhœa, and its influences, remote and immediate, are equally prejudicial to the patient. In view of the identity of their bacteriology, it is little use treating the one condition and neglecting the other, for if the former be cured, re-infection from the latter must inevitably occur.

Vaccine Treatment.—As for pyorrhœa alveolaris.

DISEASES OF THE SALIVARY GLANDS.

Bacterial disease of the salivary glands is by no means common, perhaps owing to the copious blood-

supply to the parts and the constant flushing of the parts with salivary secretion. When it does occur, the lachrymal glands may be similarly involved (Mikulicz's disease). The infective agent would appear to be a streptococcus or pneumococcus. Wright¹ has recorded the treatment of one case with a pneumococcal vaccine with only modified success. I have had under my charge one such case, due to the *Streptococcus longus*, and never want another. Prompted by considerations of the good blood-supply and ample drainage, I gave a confident prognosis, and at the end of twelve months had achieved little or nothing. The history was that over a year previously the patient, when much run down in health, had acquired a very severe ulcerated sore throat. Recovery was very slow, and left behind it a copious salivation. Numerous small ulcers appeared in the mouth at intervals, and swallowing was attended with a burning sensation. The patient was subjected to local treatment and small doses of a streptococcal vaccine without result. When I saw her, her general condition was not very good. There was a condition of advanced pyorrhœa, the left parotid and submaxillary glands seemed slightly larger than usual, but there was no pain or tenderness, and no evidence of a salivary calculus. The secretion of saliva was very profuse. I had the mouth well rinsed out with sterile water, dried the openings of the ducts with sterile wool, massaged the glands, and took film preparations and cultures. No bacteria other than a long streptococcus in considerable numbers were present. Several small ulcers were seen on the inside of the cheeks, and streptococci were also found in these.

Mr. Harry Forsyth attacked the pyorrhœa with great

¹ 'Studies in Immunization,' p. 268.

success, and within two months appeared to have brought about a cure. Mouth washes of every kind were given, and 10 c.c. of normal horse serum (antilusin of Allen and Hanbury) was taken *per os* twice daily. A vaccine was prepared and given in initial doses of 25,000,000.

At first slight improvement was apparent, but in a month or two a severe attack of the ulceration of the mucous membranes occurred. Not only were ulcers seen on the cheeks and pharyngeal wall, but from the burning pain which attended swallowing, both in the œsophagus and stomach, I have little doubt that the mucous membranes of these parts were similarly affected. Antistreptococcic serum by the mouth was alternated with the antilusin, but was entirely without effect. In about ten days the ulcers healed, but the salivation went on as before. I remade the vaccine over and over again, sterilized it with heat, with 0·3 per cent. of tricresol, with 25 per cent. galactose, by prolonged incubation, and in other ways; I used dosages varying from 25,000,000 to 500,000,000, and employed intervals varying from five to twenty-one days, but did not succeed in producing any marked improvement by the end of twelve months, when treatment was finally discontinued.

DISEASES OF THE STOMACH AND INTESTINES.

Catarrhal and Ulcerative Diseases of the Gastro-Intestinal Tract Generally.

Bacteriology.—Little work has been done on catarrhal disease of the stomach from the bacteriological standpoint. It might well be anticipated that the constant swallowing of pyorrhœic organisms would suffice to set

up this condition, and the improvement which is constantly noticed as occurring in stomach derangement when strict attention is paid to pyorrhœa alveolaris points in this direction, and indicates the necessity of routine treatment of the gums in catarrhal disease of the stomach. The few observations which have been made from the standpoint of vaccine treatment would seem to show that the streptococcus, *B. coli* and *B. acidi lactici* may be capable of setting up this condition. The reader should refer for further particulars to a paper by Dawson on 'The Microbic Factor in Gastro-Intestinal Disease.'¹ The best method for determining the infective agent in these cases is that which he there describes.

For infective catarrhal conditions of the lower digestive tract, the chief responsible agents appear to be the streptococcus, *B. acidi lactici* (Hueppe), *B. coli* and its allies, *B. pyocyaneus*, and occasionally the pneumococcus. The determination of these can only be made from observations of the fæces, and is by no means easy. Careful plating-cut experiments have to be conducted, subcultures made of all the various organisms isolated, and various serum tests applied. Of these the simplest is the agglutination test, and this usually gives sufficient indication in the case of the coliform organisms. The opsonic indices may also be estimated, auto-inoculations being perhaps induced by massage, as advised by Wright.

For the ulcerative conditions, specific organisms, such as the *B. typhosus*, *B. dysenteriae*, *M. melitensis*, or *B. tuberculosis*, may be responsible; or in sporadic cases the more common pyogenic organisms, such as *B. coli*, streptococcus, or *B. pyocyaneus*.

¹ *British Medical Journal*, April 29, 1911, p. 1124.

Preliminary Considerations.—It is hardly necessary to emphasize the fact that the resources of medical and surgical science should be thoroughly tested before the aid of vaccine treatment is invoked. The bacterial infection is rarely the primary cause; gastric dilatation, kinks and obstructions of the intestines, improper dietary, and neglect of the bowels, are the chief predisposing factors which induce invasion by the micro-organisms of pyorrhœa, or by those which are normally resident in the intestinal tract without exercising any pathogenic action. Unless these abnormalities receive attention, vaccines may produce some amelioration or even apparent cure, but relapse is inevitable sooner or later.

Vaccine Treatment.—This may perhaps be best considered under the following headings :

1. Simple catarrh.
2. Typhoid fever.
3. Dysentery.
4. Cholera.
5. Appendicitis.
6. Mucous colitis and sigmoiditis.
7. Tuberculous enteritis.

1. *Simple Catarrh.*

The number of cases, which may perhaps be grouped as ones of simple catarrh, that have been recorded as treated by means of vaccines is few. Among these may be mentioned a case described by Hale White and Eyre.¹ A woman had repeated attacks of vomiting associated with high temperatures, and an exploratory laparotomy

¹ Proceedings of the Royal Society of Medicine, vol. ii, No. 8, Therapeutic Section, p. 149.

was being considered. The stomach contents were, however, examined, and found to contain numerous coliform organisms. Under the administration of small doses of the autogenous vaccine—viz., 5,000,000 to 50,000,000—given at intervals of about twelve days, the woman made a complete recovery.

Bertrand Dawson¹ also describes two cases in which a diplo-streptococcus was found in the stomach contents. In one of these cases a diagnosis of cholecystitis and gallstones was completely disproved on operation, and no definite pathological condition found anywhere. Both cases improved considerably with vaccine treatment after failure with all other methods. In a third case associated with mucous colitis, which latter cleared up under medical treatment, resort had to be finally made to vaccine treatment. With doses of 20,000,000 of the diplococcal vaccine improvement was transitory and sometimes doubtful, but when the dose was made 30,000,000 and 40,000,000, at ten to fourteen day intervals, the improvement was definite. In the first three months of improvement the symptoms began to recur when the next dose was due, but later the patient became quite well and remained so. I have at present under my care a case of long-continued digestive trouble. Not only is the stomach dilated, but also the whole colon. The stomach contents invariably contain *B. coli*—especially numerous when bile has been regurgitated—and a short streptococcus. He reacts well to the autogenous vaccines, which he was especially desirous of trying; but inasmuch as active treatment is being also conducted on other lines, it will not be possible to estimate the effects of the vaccine treatment.

¹ *Loc. cit.*

2. *Typhoid Fever.*

Inasmuch as the portal of entry in this disease is through the intestinal tract, and the principal lesions are there situated, it is most conveniently considered now instead of in its, perhaps, more correct place among the septicæmias.

Bacteriology.—In view of the fact, which is becoming increasingly clearer, that a percentage of cases, by no means inconsiderable, is due to organisms other than the true *B. typhosus* of Eberth, exact determination should be made of the infective agent in all cases, whether vaccine treatment is contemplated or not. To the two varieties of organism most closely allied to the *B. typhosus*, the names *B. paratyphosus A* and *B* respectively have been given; to other varieties, which may give rise to conditions resembling typhoid fever in many respects, the title of ‘paracolonic bacilli’ has been given, in virtue of a closer relationship to the *B. coli communis*. Although the primary lesions are situated in the intestines, a condition of septicæmia is very soon established, and blood cultures yield a positive result in almost every case after the first two or three days. The bacteria disappear from the blood with some rapidity, so that by the end of the first week a much smaller percentage of positive cultures is obtained, even when large quantities of blood are utilized. Subsequently the bacteria may have to be isolated from the feces or urine.

The organism so obtained is identified by means of its sugar reactions, and confirmation of its identity made by comparative serum tests with this organism and another known one to which it is supposed to be similar.

If an autogenous vaccine is prepared, it should be remembered that sterility must be secured either by

heating at 53° C., but not over, for half an hour, and the addition of 0·2 per cent. trieresol, or, as Semple recommends, by the action of 0·5 per cent. carbolic acid alone, this being effective within twenty-four hours. If any greater degree of heat than 53° C. be employed, not only are the keeping properties impaired, but the immediate immunizing power is lowered.

General Considerations.—As we have seen in Chapter I., the body elaborates various antibodies to the *B. typhosus*—viz., agglutinins, lysin, and opsonin. The relative importance of these bodies is not definitely known. Formerly the chief protective rôle was ascribed to lysin; now the greater importance is assigned to opsonin and phagocytosis. By lysis the discharge is brought about of powerful endotoxins into the circulation, and it is to this cause that the continuous pyrexia of the early stages of the disease is due. The intermittent temperature of the later stages is probably due in part to the absorption of other toxins from the ulcerated surface of the Peyer's patches, and in part to the liberation of endotoxin which occurs when bacilli are dissolved before being ingested. The therapeutic use of powerful lytic sera may be fraught with danger owing to the liberation of excessive quantities of endotoxin; the therapeutic use of anti-endotoxic sera may be found to modify the severity of the disease by neutralization of the endotoxin, and the therapeutic use of vaccines, by stimulating the formation of opsonin, may be expected to influence the disease by bringing about the more speedy extinction of the bacteria within the phagocytes, the endotoxin being destroyed therein, instead of being set free in the general circulation. Its good effects are, however, limited owing to the fact that in those situations

where the bacteria are mostly stored (viz., spleen and Peyer's patches) there is exhaustion of the opsonin (see p. 123), and local conditions tend to nullify the effect of increased opsonin elaboration. It is also possible that 'complement' may be in defect, and this we know not how to make good.

Agglutinin probably plays a very subsidiary rôle, but, as we have seen (p. 16), its amount is not devoid of prognostic import. The curves of agglutinin, lysin, and opsonin, run a more or less parallel course, and inasmuch as opsonic index determinations are more than usually difficult in this disease, the 'agglutinin' curve is often substituted as a guide to the progress of immunization. In the practice of vaccine treatment reliance is now, as a rule, placed for guidance on the temperature chart and the clinical signs and symptoms.

Vaccine Treatment.—For a full account and discussion of the results obtained by himself and other observers, the reader should consult an article by Sir David Semple.¹ Papers by Stoner,² Callison,³ Watters and Eaton,⁴ Mcakins and Forster,⁵ Smallman,⁶ and Engelbach,⁷ will also afford useful information.

The procedures adopted by each differ in regard to dosages and intervals. Thus Semple originally began with initial doses of 6,000,000 to 50,000,000, but now recommends 100,000,000, this being gradually increased to 200,000,000 or 300,000,000. These he gives daily or

¹ *Journal of Vaccine Therapy*, February, 1912.

² *American Journal of Medical Sciences*, February, 1911.

³ *New York Medical Journal*, July 15, 1911.

⁴ *Medical Record*, May 6, 1911.

⁵ *Canadian Medical Journal*, June, 1911.

⁶ *Journal of Royal Army Medical Corps*, vol. xii., p. 136.

⁷ *Interstate Medical Journal*, June, 1912, p. 537.

on each alternate day, according to the clinical response. He thinks that occasional estimations of opsonin and agglutinin are useful. Callison originally employed 25,000,000, but now prefers 300,000,000, and employs estimations of opsonin and agglutinin as a guide to the progress of immunity. He believes that negative phases after such doses are either non-existent or a negligible quantity. Meakins and Forster use 1,000,000,000 as a first dose, 1,500,000,000 as the second, about eight days after the first, and 2,000,000,000 as the third dose after a similar interval. Smallman, in his earlier cases, used 100,000,000 as his first and second doses, the interval being nine to ten days. Later he used doses of 300,000,000 at shorter intervals with better results. Sadler¹ prefers an initial dose of 2,000,000, a second five days later of 1,000,000, this dosage and interval being continued subsequently. Alternatively he advocates doses of 300,000,000.

Summarizing the matured opinions of those who have had the greatest experience, it would appear that the best initial dosage is one of 250,000,000 to 300,000,000, which may be safely repeated at intervals of three to five days, according to the immunizing response and the clinical condition of the patient.

There is some difference of opinion as to whether 'stock' or autogenous vaccines give the best results. Some prefer a stock vaccine made from a strain such as we shall see is employed for preparing the vaccine for antityphoid immunization—viz., a long-cultured strain which has lost almost all pathogenic powers, but still possesses a strongly immunizing action. Others prefer a polyvalent stock vaccine made from fully virulent

¹ *Journal of Vaccine Therapy*, vol. i., No. 1, p. 17.

strains, not only of the *B. typhosus*, but also of the paratyphoid bacilli. Others much prefer the autogenous vaccine in every case. Inasmuch as mixed infections by the *B. typhosus* and a paratyphoid bacillus are not unknown, and purely paratyphoid infections are fairly common, I think the wisest procedure is to employ for the first dose or two a stock polyvalent vaccine, containing the *B. typhosus* and *paratyphosus*, proceeding meanwhile with the preparation of the autogenous vaccine, and to utilize this for subsequent inoculations.

The Results of Vaccine Treatment.---The immediate results of inoculation with a vaccine are best seen in the severely toxic cases. Within twenty-four hours there should be, in the majority of instances, a decided improvement in the general condition, a lowering of the temperature and pulse-rate, a clearing of the mind, and evidence of greater comfort of the patient. A retrogression in any one of these directions is the signal for reinoculation. Occasionally improvement is delayed until the second day ; in this case reinoculation may be deferred for two or three days, or until retrogression is observed ; but if no improvement is discerned by the end of forty-eight hours, the immediate administration of a double dosage is advisable. Treatment should be continued till the lapse of three to four weeks after complete defervescence, in order to secure the destruction of any bacilli which may still be lurking in the tissues.

The observed influence of vaccine treatment upon the mortality and liability to relapse are best shown in tabular form on p. 211.

The number of cases so far recorded is too small to allow of a definite comparison being drawn between the results obtained by treatment with vaccines, and those

obtained when treatment is conducted according to the usual routine principles. Both the mortality rate and the percentage of relapses vary greatly from time to time. The former varies between 10 and 20 per cent., the mean of 15 per cent. being a fair average. Relapses occur on the average in 20 to 25 per cent. of cases. The figures given below—viz., 4.1 per cent. for the death-rate and 3.9 per cent. for relapses, would seem to leave a very appreciable balance to the credit of vaccine treatment.

Observer.	Cases.	Deaths.	Relapses.	Per Cent. of Deaths.	Per Cent. of Relapses.
Semple	60	2	2	3.3	3.3
Stoner and Callison	266	12	11	4.5	4.1
Watters and Eaton	36	—	3	—	8.3
Meakins and Forster	41	1	1	2.4	2.4
Smallman ..	36	3	—	8.3	—
Total ..	439	18	17	4.1	3.9

The unanimous opinion is that vaccines are quite innocuous when properly used, and that no aggravation or injury of any kind results from their use; but that, on the contrary, they confer distinct benefits on the patient, by diminishing the toxæmia, shortening the duration of the disease, reducing the mortality, and diminishing the liability to relapse.

Typhoid Carriers.—As the amount of study that is devoted to the elucidation of the causation of typhoid epidemics accumulates, the more increasingly clear does it become that in many instances such epidemics are initiated by contamination of the food and drink at the hands of those who prepare or supply it. These individuals continually harbour the *B. typhosus* somewhere in their bodies, usually in the gall-bladder or

kidneys, and are accordingly known as 'carriers.' In the great majority of these a history of a definite attack of typhoid fever is usually obtainable. As a rule, convalescence is uninterrupted, though perhaps rather prolonged, and recovery apparently complete. The detection of these carriers is thus a matter of great concern. It is likewise one of no little difficulty owing to the fact, first demonstrated by Semple, that the discharge of bacteria may be very intermittent. It has been stated that it is impossible to declare with certainty that anybody who has recovered from an attack of typhoid fever has not become a carrier unless careful bacteriological examinations of the urine and fæces, conducted at weekly intervals for at least one year, fail to detect the presence of the bacilli. Semple's view that the storage of organisms takes place in the liver and kidneys has been confirmed by numerous other observers. Some of the investigations are of particular interest. Alice Hamilton¹ examined twenty-four persons with a history of gall-bladder trouble. Determinations of the opsonic index of the sera, after these had been heated at 58° C. for fifteen to twenty minutes, showed that seven out of the twenty-four had constantly abnormal indices to the typhoid, or a paratyphoid, bacillus. Of these, those who had acute gall-bladder symptoms had a fluctuating index, the others had a persistently high one. All these seven individuals were proved to be carriers, five of a paratyphoid bacillus, two of the *B. typhosus*. In only five out of the seven was the Widal reaction obtained. Of the seventeen non-carriers, none had an abnormal index, nor gave a Widal reaction in a

¹ *Journal of American Medical Association*, February 26, 1910, p. 704.

1 in 50 dilution. Hamilton claims that index determinations are trustworthy, and much simpler than bacteriological examinations of the urine and fæces.

It has occurred to me that much the simplest method of detection would be to do a 'Calmette's reaction' on the eye, using, not an emulsion in water of the dead bacillus, as has been done for the diagnosis of active typhoid fever, but a preparation of endotoxin made by MacFadyen's method. In order to prove the reliability of this method, it will be necessary to make comparisons in a large number of cases, not only of those who are shown by direct observation to harbour the bacillus, but also of those who have made complete recoveries.

Although the liver and kidneys are the chief lurking-places of the *B. typhosus*, they are by no means the only ones. Thus Cammidge¹ records the detection of the bacillus in the stools of a case of pancreatic glycosuria, a sufferer ten years previously from typhoid fever. In this case the nidus would appear to be the pancreas. The bacilli have also been recovered from bone abscesses, which have appeared long after apparently complete recovery from typhoid fever. Sir Hector Cameron² records one such case twenty-seven years afterwards. Other cases have been recorded six and ten years afterwards. It is an interesting question whether the routine treatment of typhoid fever, by means of vaccines, well into convalescence would not do much to diminish the number of these carriers, the existence of whom is such a source of continual danger to the whole community.

Vaccine Treatment of Carriers.—Ordinary methods of treatment have proved entirely ineffectual in these cases,

¹ *Lancet*, January 19, 1909, p. 1739.

² *British Medical Journal*, April 29, 1911, p. 975.

but in a few instances success has attended vaccine treatment. The first case to be so treated was reported by Irwin and Houston.¹ It was that of a carrier of seven years' duration, who was excreting large numbers of bacilli in the urine, but none in the fæces. An injection of 50,000,000 produced rise of temperature, malaise, and headache. Double this dose eight days later produced a milder reaction, and was followed eighteen days later by one of 200,000,000. Two days after the third injection the urine was crowded with bacilli. The urine was rendered alkaline, and eighteen days later the *B. typhosus* had disappeared from the urine. Further doses of 300,000,000, 500,000,000, and 1,000,000,000, were given at intervals of fourteen days. The agglutination test was only obtainable then in the 1 in 10 dilution, instead of in one of 1 in 200, as formerly. There was considerable improvement in the general health, and the patient gained 10 pounds in weight. Although observations have been made of the urine for over two years, the *B. typhosus* has never again been detected. Houston² has since treated three more similar cases. In two of these complete cure appears to have been brought about, the other one has been markedly improved.

Inasmuch as results equally successful with those obtained by Houston have been achieved by Dickson³ and other observers, it would appear that in vaccines we have the only practical means of ridding 'carriers' from their infection, though at times this treatment will also fail.

Antityphoid Inoculation--Methods of Preparing the Vaccine.—The method approved by the Army Council

¹ *Lancet*, January 30, 1909, p. 311.

² *British Medical Journal*, 1909, vol. ii., p. 1056.

³ *Ulster Medical Society*, May 10, 1911.

for use in the British Army is as follows : A layer of broth, 1 to 1½ inches in depth, is placed in special flasks of such a form that maximum aeration is secured. The medium is inseminated with a special strain of the bacillus which has lost almost all its virulence, even for animals. Incubation is conducted at 37° C. for thirty-six to forty-eight hours, when the growth is sterilized at 53° C. for one hour, sterility being observed by means of aerobic and anaerobic cultures, and 0·4 per cent. of lysol is added to insure absolute sterility. The vaccine is standardized in the usual manner in duplicate.

Semple advises that sterility should be secured without the aid of heat, and states that this is secured after twenty-four hours' admixture with 0·5 per cent. carbolic acid.

Castellani prefers a vaccine which has been heated to 50° C. for half an hour. This contains still living but greatly attenuated bacteria.

Vincent advises the following procedure : The bacteria, which consist of typhoid and paratyphoid strains, are grown on a solid medium and removed therefrom and allowed to autolyze in 0·9 per cent. sodium chloride solution. The mixture is well centrifugalized, and the clear supernatant liquid removed, mixed with ether, and well agitated, the ether being removed by heating to 37° C. for a few minutes. This vaccine is practically free of bacterial bodies, and is a solution of endotoxins.

The vaccine used in the English, French and American Armies is prepared according to the first of these procedures ; the subsequent methods have been devised to improve the keeping properties, as when the first method is employed it is found that the power to incite the formation of opsonin, lysin, and agglutinin, begins to decline after three months, and falls off rapidly after six months.

The Procedure of Immunization.—This varies slightly in different countries, and with different authorities. The present procedure in the English Army is to repeat the first dose of 500,000,000 on the tenth day; in the American Army, 500,000,000 and 1,000,000,000 are given in succession at intervals of nine days; in the French Army four doses are given. Inoculations are given subcutaneously at any of the sites given on p. 108. Castellani, who formerly administered 0·5 c.c., 1 c.c., and 1·5 c.c. of his vaccine at intervals of a week, now advises that a 500,000,000 dose of a vaccine prepared according to the first method should be followed a week later by 1 c.c. of his own preparation, and claims that thereby a higher degree of immunity is secured.

Effects of Inoculation—

1. *Locally.*—Tenderness begins to make itself felt in five or six hours, and is at its worst in about eighteen hours, when there may be developed redness over an area of 2 inches radius. Occasionally the lines of the lymphatics may be traced, and some tenderness of the corresponding lymphatic glands. These should all pass away within forty-eight hours.
2. *Generally.*—Some degree of malaise is usually produced. In a small percentage of cases there is a tendency to faintness; occasionally a rigor comes on between the first and sixth hours; rarely there is diarrhœa, vertigo, or a slight diffuse erythema. There is always a slight degree of pyrexia, usually to 100° F., occasionally to 101° F., and rarely to 103° F., which generally subsides by the end of twenty-four hours.

Formerly it was stated that there was a marked reduction of opsonin, lysin, and agglutinin, in the serum for several days, followed by a greater rise.

This 'negative phase,' which was formerly regarded as strongly contra-indicating immunization either during an epidemic or when exposure to infection would occur within a few days, is now characterized by Leishman, Russell, and others, as a pure bogey. Thus Leishman points out that during a recent very severe epidemic at Maidstone, the attendants were all immunized at the time, yet not one contracted the disease; also that typhoid is always endemic in India, and that the garrisons are accordingly exposed to infection during immunization, yet no epidemic is encountered.

The duration of the immunity thus conferred has been studied by Harrison¹ and others. They have found definite evidence of increased antibodies in the serum of men who had been inoculated as long as six years previously. Leishman believes that full immunity is maintained for two years.

The Results of Immunization.—Much discussion has taken place in the past as to the merits of the procedure. Recent evidence is, however, greatly in its favour. For instance, during manœuvres of the American Army at San Antonio the whole strength of 12,639 men were inoculated, with the result that only one mild case occurred during the whole four months, although among the populace there were 49 cases and 19 deaths. Among a force of between 3,000 and 4,000 who were encamped at Galveston, and received the same food, milk, and water supply as the inhabitants of the city, there was not one case of enteric. Among the inhabitants during the same

¹ *Journal of Royal Army Medical Corps*, 1907, p. 472.

time there were 192 cases. During the preceding manœuvres in Florida, which were conducted at the same time of year and under precisely similar conditions, the water-supply coming from an artesian well of accepted purity, 10,739 men, who were not inoculated, were engaged; 1,229 cases occurred, and 248 deaths: the significance of these figures is, however, in dispute.

In India, as the proportion of the army voluntarily undergoing immunization increases, it is noted that both the number of cases and of deaths shows a steady and marked decrease; at the same time it must be admitted that the increased attention given to the 'carrier' question cannot be without its effect. In the following table are set out the rates of typhoid fever, and of deaths therefrom, and the ratio per 1,000 of men inoculated in the army in India from 1906 to 1910 inclusive:

Year.	Typhoid Rate.	Death-Rate therefrom.	Ratio of Men inoculated per Thousand.
1906	15.6	3.19	66
1907	13.1	2.77	143
1908	14.5	2.76	225
1909	8.9	1.58	613
1910	4.6	0.63	823

Thus the typhoid rate has fallen in five years from over 15 to under 5 per 1,000, and the death-rate from over 3 to 0.63 per 1,000. During 1910, among about 70,000 men, there was a total of 306 cases of enteric; 151 of these occurred in the 10,000 who were unprotected, and only 155 in the 60,000 who were. Only 11.2 per cent. of the inoculated died, and 16.1 per cent. of the uninoculated.

Finally, of the 16,496 men of the German Army who

took part in the Hereros campaign from 1904 to 1907, 7,287 were inoculated, and 9,209 not. There were 1,277 cases of enteric altogether. Among the inoculated the incidence rate was 5·09 per cent., and the death-rate 6·47 per cent. Among the uninoculated the incidence rate was 9·84 per cent., and the death-rate 12·8 per cent. These various statistics must surely place the value of the proceeding beyond all further question.

3. *Dysentery.*

Of the two forms of dysentery, the one with which vaccine treatment is concerned is the bacillary alone. Several closely-allied bacteria, differing mainly in their sugar and agglutinative reactions, have been described in different epidemics by Shiga, Kruse, Flexner, Hiss, and Strong, and bear their respective names.

The chief work from the point of view of immunization by means of vaccines has been done by Captain W. H. C. Forster, of the Indian Medical Service. During the past few years he has been actively engaged upon the subject, and to his publications and letters I am indebted for the following account :

Clinically, bacillary dysentery may be divided as follows :

CLASS I. Acute dysentery—

1. Gangrenous.
2. Non-gangrenous.

CLASS II. Chronic dysentery, which may be subdivided into—

1. Cases of weeks' or months' duration, in which the patient is still passing dysenteric stools, either continuously or intermittently.

2. Cases of years' duration, in which the patient has ceased to pass dysenteric motions, and in whom the symptoms consist of flatulent diarrhœa, accompanied by abdominal pain of a peculiar type.

Of these, the following are suitable for vaccine therapy :

The non-gangrenous cases of Class I., which have resisted treatment for seven days, and in which the patient is not obviously moribund.

Of Class II. all cases are suitable except those in whom the bowel is so extensively damaged by chronic ulceration as to render hopeless treatment of any sort.

Although the cases treated have been variously infected by the following different strains—Kruse-Shiga, Flexner, and Y. of Hiss—the vaccine employed has been prepared only from the Kruse-Shiga type ; so that the results achieved are the more striking. Uniformly satisfactory results have been obtained and recorded by Forster,¹ Gillitt,² Stephen,³ Newman,⁴ Castellani,⁵ and Shivdas,⁶ many of the cases being very striking, especially the chronic relapsing ones, in which all medical treatment had been unavailing. Thus, of ten such chronic cases, Forster completely cured seven, these remaining perfectly well for twelve months after treatment.

In the Midnapore Gaol the case mortality over six years averaged 6·3 per cent. After the adoption of Forster's vaccine it fell to 0·9 per cent.

¹ *Indian Medical Gazette*, June, 1907, p. 201.

² *Ibid.*, January, 1908, p. 12. ³ *Ibid.*, October, 1907, p. 375.

⁴ *Lancet*, May 16, 1908, p. 1410.

⁵ *Archiv f. Schiff u. Trop. Hyg.*, Bd. xi., Heft 3.

⁶ *Journal of Vaccine Therapy*, vol. i., No. 4, p. 112.

The scheme of treatment laid down by Forster is as follows : The immediate injection of acute as well as of chronic cases by means of a stock vaccine, given in small doses at fixed intervals, without the control of the opsonic index. Of course, common sense must be applied if clinical symptoms contra-indicate the repetition of a dose at a given time. In acute cases the commencement of vaccine therapy is contra-indicated from the fourth to the twenty-first day, during which interval the anti-endotoxic sera of Kruse and Shiga may be given in full doses frequently repeated.

As different strains of the organisms vary greatly in their toxicity, and as toxic strains are liable to produce very violent local and general reaction, even in small doses, counting methods of standardization are not employed, but the strength of the vaccine is so regulated that the minimum lethal dose for a rabbit of 1,200 to 1,400 grammes in weight is not less than 0·4 c.c. Of such a vaccine his dosages are, for an adult, in both the acute and chronic forms—

First dose	..	..	..	..	0·1 c.c.
Second dose	..	..	..	..	0·2 c.c.
Third dose	..	..	..	..	0·3 c.c.
Fourth dose	..	..	..	..	0·4 c.c.

For females a slight reduction is necessary.

In the case of a child of nine, a first dose of 0·05 c.c. was given, and a second of 0·1 c.c., without ill effects and with a good result.

The doses indicated above produce practically no negative phase, and in fourteen days the immunity is more than a hundred times what it was before the dose.

Ruffer has prepared a vaccine by treatment of the

bacilli with peptic ferment, and found that, while the toxic effects are thereby much reduced, the immunizing response, as judged by animal experiments, is painlessly and rapidly produced, and is of a very high degree.

Forster employs intervals of ten days between the doses, and usually proceeds to the fourth dose, to make sure that the patient has got rid of all bacilli and is not likely to become a chronic 'carrier.' If it be necessary to go beyond the fourth dose with increased quantities, the bowel symptoms must be carefully watched, as large doses are very toxic, and in animals, at all events, badly tolerated. In man, the symptoms of overdosage take the form of dysenteric pains in the bowel, with diarrhœa and even blood and mucus. Most doses are followed by some slight symptoms of the sort, but if these are severe in any given case, a reduced dosage must be employed.

Vaccine treatment would appear to hold out promise of success in the case of summer diarrhœa of infants, and in asylum dysentery. In both these a certain percentage of the cases are due to the *B. dysenterix*. These would almost certainly benefit. In the others an auto-genous vaccine of the causative organism should certainly give the best results, but the use of a stock vaccine of the Kruse-Shiga bacillus has been found to be of distinct utility in a certain number of cases, where the infective agent was not that particular strain, but a more or less closely allied one.

4. *Cholera*.

Immunity against the cholera vibrio appears to depend almost entirely on lytic action, though opsonin and phagocytosis may play some part.

The vaccine therapy of this infection is at present confined to preventive inoculation. During an actual attack it appears to be of no avail.

In anticholera vaccination, as devised and practised by Haffkine, use is made of two vaccines, the stronger one of which is prepared from organisms whose virulence has been exalted by growth in the peritoneal cavity of guinea-pigs, the passage being continued until a culture is obtained which is invariably fatal to these animals within eight hours. This is known as the 'virus fixe,' and is used to inseminate agar slopes, which are incubated at the optimum temperature for growth—viz., 35° C. The weak vaccine is prepared by growing an ordinary laboratory culture in broth at 39° C., a constant current of air being maintained. Its sterility is tested day by day until subcultures upon agar no longer show growth. The last subculture that grew is then taken and grown on agar slopes, 10 centimetres long, at 39° C., in a current of air.

The agar cultures for both strong and weak vaccine are treated as follows : 6 c.c. of 0·5 per cent. carbolic acid solution are added to each tube, and the bacterial contents thoroughly emulsified ; 1 c.c. of the preparation constitutes a dose. The weak vaccine is first injected, and may be repeated after an interval of three days, the strong one being given five days later. Full immunity is attained in five or six days after the last injection, and is said to persist for about a year.

Kolle advises the use only of a vaccine of the fully virulent organisms, and finds that the local necrotic effects which were anticipated do not occur.

The good results are seen in a reduction of the incidence of the disease, and not of the case mortality, which appears

to be uninfluenced. This may be seen in the table given below, which is compounded of the recorded results from numerous sources spread over several years :

Class.	Numbers.	Cases.	Deaths.	Fatality.
		Per Cent.	Per Cent.	Per Cent.
Uninoculated ..	18,355	667 = 3·6	393 = 2·1	59
Inoculated ..	12,744	84 = 0·66	48 = 0·4	57

5. *Appendicitis.*

Although the organism most commonly concerned in inflammatory conditions of the appendix is the *B. coli*, in a small percentage of cases practically pure cultures of the streptococcus, pneumococcus, or *B. pyocyaneus* have been obtained from the inflamed mucous membrane or the pus of an abscess. Bertrand Dawson¹ has well pointed out the connection which often exists between attacks of appendical pain and a septic condition of the gums and tonsils. He says: 'I have satisfied myself that there is sound clinical evidence for the existence of this association between inflammations of the tonsils and appendix. Not only is the sequence of the two events met with, but removal of an appendix will sometimes cure a chronic throat.' He then points to the observations of Hasse, that in an institution within two months there occurred thirty cases of appendicitis, mostly following on tonsillitis; of Backhammer, that eight cases of suppurative tonsillitis occurred along with appendicitis; and of Apolant, of Jessen, and of Weber to the same effect.

Surely the lesson that is to be learnt from this is that in all cases of appendicitis the gums and tonsils should

¹ *British Medical Journal*, April 29, 1911, p. 1129.

be most carefully scrutinized, and, if time permits, measures should be taken to remedy any septic condition there, vaccines being employed under the conditions already described (see *Pyorrhœa Alveolaris* and *Diseases of the Tonsils*, pp. 195, 200), in the hope that recurrence of the appendical pain may thus be obviated. Dawson¹ refers to a parallel case of recurrent pharyngitis associated with recurrent mucous colitis. The pharyngitis was due to a pneumococcus, and a vaccine prepared therefrom improved both conditions; and when suitable doses were exceeded, both conditions were temporarily aggravated.

It has also been suggested that a vaccine of *B. coli* should be employed as a routine in the following way: When a case does not appear to stand in need of immediate operation, the opsonic index to the *B. coli* should be determined. If it be found to be abnormally low, then 25,000,000 to 50,000,000 doses of the vaccine should be given, in order to diminish the risks of complications if subsequently operation proves necessary, and in the hope that spontaneous recovery may occur, in which event the patient's immunity should be raised by a full course of inoculation, which may advantageously be repeated at regular intervals of six to twelve months. When pus is found at appendicitis operations, it will prove a useful safeguard if cultures are always taken and held in reserve for the immediate preparation of a vaccine should any complication ensue. In the cases where this is more or less localized, the vaccine treatment should be conducted on the lines already laid down (see *Abscess, Fistula, etc.*, pp. 137, 155). If the peritoneal cavity become infected, the procedure will be that subsequently described under *Septicæmia* (see p. 263).

¹ *Loc. cit.*

6. *Mucous Colitis.*

Bacteriology.—A considerable amount of research has been done on the bacteriology of this very intractable complaint by Matthews, Eyre, and others. The procedure has been either to take direct cultures through a sigmoidoscope, or to select a suitable piece of mucus from a motion, wash it well with sterile salt solution, and then use it to inseminate plates of suitable culture media, which will facilitate the isolation of the various coliform bacilli, *B. pyocyaneus*, streptococci, and pneumococci. The different organisms are then tested as regards their serum reactions, Matthews preferring to rely on opsonic index estimations, Eyre rather on the agglutination test. Those organisms, which give abnormal results, are considered to be concerned in the disease. Matthews then massages the colon and looks for the effects of an auto-inoculation. This procedure is condemned by others on the score of danger to the patient from too forcible manipulations.

As with appendicitis, so here the organism to which most commonly pathogenic action is to be attributed is a member of the coli group, less frequently the *B. pyocyaneus* or *B. acidi lactici*, and still less frequently the bacillus of Friedländer, a streptococcus, or pneumococcus.

Preliminary Considerations.—What has been already said with regard to the association between septic conditions of the mouth and pharynx and appendicitis holds with equal force in regard to mucous colitis. Treatment should always first be directed to the cure of this undoubtedly predisposing factor. If this be achieved, and due attention be paid to malposition of the abdominal

viscera, to errors of dietary, and the regulation of the bowel functions, the necessity for specific immunization will be correspondingly reduced. Another strongly predisposing factor which should always receive prior attention is any pathological condition of the female generative organs.

Vaccine Treatment.—Favourable reports have now been made of the use of autogenous vaccines, prepared from organisms selected in the way just described, by numerous observers, among whom may be mentioned Butler Harris,¹ Eyre,² Willcox,³ Matthews, and B. Dawson.⁴

In view of the fact that large doses may produce rigors and vomiting, and so possibly hæmorrhage and collapse, it is well to begin with quite moderate doses of the various vaccines. Thus Butler Harris employs doses of 10,000,000 *B. coli* at weekly intervals, and states that 'the patients soon put on weight, improve in general health, and pass no more blood or mucus. Several of them are now well for over two years; two others, however, require occasional inoculation. The patients know when they are losing ground, and present themselves for treatment. I venture to think that in severe cases of colitis, appendicostomy, followed by vaccine treatment, would be the most desirable course to adopt. Certainly inoculation gives better results than washing out by the bowel.'

Hale White describes the case of a young man aged seventeen, who had suffered from ulcerative colitis for many years, and in whom every form of treatment had been tried but opening the appendix and vaccine treatment. A vaccine of his *B. coli* was tried, with the result

¹ Proceedings of the Royal Society of Medicine, vol. iii., No. 9, p. 104.

² *Ibid.*, p. 63.

³ Harveian Society, March 9, 1911.

⁴ *Loc cit.*

that the temperature immediately began to fall, the motions became more normal, the passage of blood ceased, and he is now well, of normal weight, and earning his living. He finds that the results are not always so striking as this, and that progress is often very tedious, and that very often several forms of treatment have to be conducted simultaneously.

Willcox has found autogenous vaccines of decided help in cases which do not respond to ordinary medical means, and holds that they should always be tried before the abdomen is opened, except in very acute cases.

Dawson describes three cases in which at least considerable improvement was brought about. While convinced of the good results, he yet feels that bacterial infection is not the only cause of colitis, but that it is rather a direct causal factor of varying import, in some cases more dominating, and in other cases less dominating.

In conclusion, it may be said that while every case must be treated entirely on its own merits, and with due regard to all its clinical features, the cautious use of vaccines in small to moderate doses will almost certainly be productive of considerable improvement. Relapse will require to be guarded against by a short course of treatment at more or less regular intervals.

7. Tuberculous Enteritis and Peritonitis.

The main consideration which should, I think, guide in the consideration of the question whether vaccine treatment is to be applied or not in these conditions is whether the abdominal condition is primary or secondary to tuberculous disease of the lungs. The only three cases of enteritis and peritonitis which I have seen in as many years were all secondary to lung trouble, and were

terminal infections, induced, I cannot but feel, by the oral administration of tuberculin before they came under my care. In such cases as these tuberculin treatment is foredoomed to failure. In primary cases it is quite another matter, and the outlook is a much more hopeful one. Despite this, the number of cases recorded in which this treatment has been followed remains relatively small.

Turton records a case in which laparotomy revealed such extensive disease of the cæcum and ileum that removal was impossible. Thirty-eight injections of T.R. and twenty-one of *B. coli* vaccine were given in six months, with the result that the patient gained 16 pounds in weight, and the tumour, which was the size of a goose's egg, entirely disappeared. The patient returned to work, and at the end of a year had only had very rare attacks of pain of a very mild character.

Of peritoneal cases quite a fair number have been treated with tuberculin.

Jones¹ gives the results obtained in six cases after about six months' treatment at St. Mary's Hospital as follows: None are cured, but three are much better; one of these is free from pain, and has been discharged. The other three have improved slightly.

Murdoch² treated fifteen cases with tuberculin, and found that the abdominal masses had in many cases disappeared. The patients had put on weight and improved in general health.

Warren Crowe has treated three cases, one being a very severe case with uncontrollable diarrhœa, slight pyrexia, rapid pulse, and severe anæmia. From the first dose of

¹ *Loc. cit.*, p. 115.

² *British Medical Journal*, 1911, p. 439.

0.00001 c.c. T.R. he began to improve, and, like the other two, made a good recovery.

Raw states that he has treated eight cases, four being of the dry plastic variety, and four associated with fluid in the abdomen, and that all have recovered after twelve inoculations.

Other isolated instances of remarkable cures have been recorded, and it would appear that at times striking results may be brought about. In cases with much exudate, laparotomy or repeated aspiration would appear to be indicated in order that the exudate, which Wright has shown to be very deficient in immune bodies, may be replaced by a more active fluid. The initial dose of T.R. may be 0.00001 c.c., and is to be gradually increased as the clinical condition indicates. The interval between injections should be seven to fourteen days.

DISEASES OF THE LIVER AND GALL-BLADDER.

In bacterial diseases of the liver the infection is borne either by the hepatic artery, portal vein, or bile ducts. In the first instances they form part of a general pyæmia, and their treatment will be part of that for the pyæmia (see p. 263). In the second instance they are secondary to a gastric ulcer, appendicitis, ulcerative conditions of the intestine and pelvic suppurations. Here also their treatment will be more or less included in that of the primary focus. In the third instance the infection is chiefly effected in consequence of ulceration, due to gall-stones. It may also be secondary to an infective condition of the pancreatic ducts spreading into the bile ducts.

The vaccine treatment of these parts is chiefly con-

cerned in the treatment (1) of a chronic infection of the liver and bile ducts by the *B. typhosus*—i.e., of a typhoid 'carrier' condition (see p. 211); (2) of a cholangitis and hepatitis due to the *B. coli*, either secondary to gall-stones, or to some other condition. The services of the vaccine therapist may then be called upon to assist the surgeon in relieving the patient of his bacterial infection. Wright has suggested the advisability of trying vaccine treatment primarily in cases of recurrent pain referable to the pancreas or gall-bladder, in which definite evidence of the presence of gall-stones is lacking.

In post-operative cases the bacteriological diagnosis is simple, and the treatment best conducted with the auto-genous vaccine. 10,000,000 streptococci or 25,000,000 *B. coli* would be appropriate initial doses, and their repetition or increase will be guided by the clinical condition and temperature chart.

DISEASES OF THE PANCREAS.

A considerable stimulus has been given to the vaccine treatment of pancreatic disorders by two observations: (1) That the vaccine treatment of boils and carbuncles in diabetics almost invariably results in a simultaneous improvement of the diabetes; (2) that acute and especially subacute pancreatitis is a much more common disease than was formerly thought to be the case. The diagnosis of these conditions has been much facilitated by Cammidge's observations on the urine and fæces, and the device of his so-called 'pancreatic reaction.' Bacteriological investigations have shown that bacteria, and especially the *B. coli*, are intimately concerned in these conditions.

Seven cases of diabetes, in which the exhibition of a *Staphylococcus aureus* vaccine, prepared from organisms isolated from concurrent carbuncles, produced marked amelioration of the glycosuria, have been reported by Shivdas,¹ three by Miller,² and three by MacWatters.³ Doses of 100,000,000 to 500,000,000 of an autogenous *Staphylococcus aureus* vaccine, prepared either from a carbuncle or diabetic ulcer, and given at intervals, varying from three to ten days, but mostly of seven days, were employed by each.

The results may be tabulated as follows :

Observer.	Dose and Intervals.		Duration of Treatment.	Effect on Sugar.
	Millions.	Days.		
Shivdas	100-300	8	2 months	4 per cent. disappeared.
„	150-250	8	10 days	4 per cent. disappeared.
„	125-250	6, 10, 15	6 weeks	3 per cent. fell to $1\frac{1}{2}$ per cent.
„	250-500	8	2 months	2½ per cent. disappeared.
„	100-250	10	3 „	4 per cent. fell to 1 per cent.
Miller	250-1,000	7	2 „	abundance disappeared.
„	250-5,000	7	1 month	? amount disappeared.
„	300	7	1 „	considerable amount disappeared.
Mac-Watters	200	7	3 weeks	2 per cent. disappeared for six months, then 0.5 per cent.
„	300-500	7	3 months	9 per cent. fell to a trace.
„	250-500	5		16 ounces fell to 2 ounces—death.

¹ *Journal of Vaccine Therapy*, vol. i., No. 4, p. 100.

² *Ibid.*, vol. i., No. 5, p. 157.

³ *Proceedings of the Royal Society of Medicine*, vol. iii., No. 9. Supplement, p. 178.

In two other cases of Shivdas's, of which details are not furnished, the sugar completely disappeared. Thus, in eight cases out of thirteen, there was a complete disappearance of the sugar, and in two more it was reduced to a mere trace. Whether six of Shivdas's cases were in actual diabetics, or whether the glycosuria was more or less merely coincident with the carbuncles, is not clear; the probability is that one or more of them were truly diabetics. The seventh was a case of diabetic gangrene. In all, apparently, complete restoration to health was brought about, and in five instances the sugar disappeared completely. Two of Miller's and all MacWatter's cases were undoubtedly diabetics, yet each of the former's and two of the latter's made practically complete recoveries, despite the fact that the diet was not restricted.

It would thus appear, from this limited number of cases, that vaccine therapy is capable of doing more for diabetic subjects than is any other form of treatment. It is, of course, probable that other organisms besides the *Staphylococcus aureus* may be responsible for the condition, and it is quite possible that a combined vaccine containing *B. coli*, as well as staphylococcus, would give even better results.

Experimental data are as yet lacking as to the effect of a vaccine of *B. coli* in cases of acute and subacute pancreatitis; but it would appear that there here exists a most profitable field for research.

PERITONITIS, ACUTE AND CHRONIC.

Bacteriology.—For acute peritonitis almost any of the pyogenic bacteria may be responsible. The most common organism is probably the *B. coli*, next the pneumococcus,

while streptococci, *B. pyocyaneus*, and staphylococci, are less frequently found. The condition is usually set up by a perforating ulcer of the intestinal tract, or by an acute endometritis, and is commonly accompanied by a general septicæmia. The vaccine treatment is that suited to a case of acute endometritis or general septicæmia (see p. 263). Operative interference will be practically inevitable. Little resort appears so far to have been made to vaccine treatment in this condition, an omission which is much to be regretted in view of the very excellent results which have been obtained in septicæmias generally. One case of primary diffuse peritonitis in a child of eight was operated on and treated with vaccine in doses of 10,000,000 to 25,000,000 at intervals of five or six days.¹ The surgeon considers that the vaccine contributed largely to the successful issue.

Chronic Peritonitis.—See *Tuberculous Enteritis*, p. 228.

¹ *British Medical Journal*, March 13, 1909, p. 651.

CHAPTER VIII

DISEASES OF THE GENITO-URINARY SYSTEM

Disease.	Organisms Associated with It.
Pyelitis and nephritis (acute)	<i>B. coli</i> , streptococcus, pneumococcus, staphylococcus, <i>B. pyocyaneus</i> .
Pyelitis and nephritis (chronic)	<i>B. tuberculosis</i> (primary), pyogenic bacteria (secondary), <i>B. coli</i> .
Cystitis (acute) ..	<i>B. coli</i> , pneumococcus, streptococcus, staphylococcus, etc.
Cystitis (chronic) ..	<i>B. coli</i> , <i>B. tuberculosis</i> (primary), pyogenic bacteria (secondary).
Urethritis	} acute .. { Gonococcus, staphylococcus, streptococcus, pneumococcus.
Epididymitis	
Orchitis	
Vesiculitis	
Urethritis	} chronic { <i>B. tuberculosis</i> , except in case of urethritis, where the pyogenic organisms and bacillus of Friedländer, <i>B. influenzae</i> , etc., are responsible.
Epididymitis	
Orchitis	
Vesiculitis	
Vulvo-vaginitis ..	Gonococcus, staphylococcus, streptococcus, etc.
Metritis, endometritis, and salpingitis (acute)	Gonococcus, <i>B. coli</i> , pneumococcus, streptococcus, staphylococcus, etc.
Metritis, endometritis, and salpingitis (chronic)	<i>B. tuberculosis</i> (primary), pyogenic bacteria (secondary); also gonococcus, <i>B. coli</i> , etc.

We thus see that in chronic infections of all parts except the urethra and vagina the *B. tuberculosis* is very commonly present as the primary invader, pyogenic cocci being frequently superadded as secondary infections. The vaccine treatment of tuberculous infections of these

parts may therefore be conveniently described under the heading of 'Tuberculous Disease of the Genito-Urinary Tract.'

PRELIMINARY CONSIDERATIONS.

From the above table it is clear that a great variety of organisms may be responsible for the acute infections of the genito-urinary tract. Inasmuch as many of these are normal inhabitants of the parts, or of parts adjacent to them, considerable care is necessary to determine the true infective agent. Thus, in the investigation of a case of endometritis it is hardly sufficient to take a swab from the cervix through a speculum without thorough prior flushing out of the vagina with sterile water, and in a case of nephritis it will not suffice to collect the last part of a voided urine in a sterile vessel, nor even to collect it by catheterization of the bladder; but the bladder should be first emptied naturally, then the urethra and bladder should be well flushed with sterile salt solution, and the urine collected from each kidney by catheterization of the ureters. Other necessary precautions will suggest themselves to the careful investigator. After proper collection of the specimen, direct examination of smears should be made, and appropriate cultural methods performed, to the end that each variety of bacterium should be secured in pure growth. If necessary or desirable, serum tests should then be made to determine what organisms are responsible for the lesions.

ACUTE NEPHRITIS.

This may be conveniently subdivided into Ascending Nephritis, Nephritis of Pregnancy, Nephritis in Children.

The bacteria concerned in an *Ascending Nephritis* will obviously be determined by the nature of those

present in the primary focus, which is usually the bladder. The vaccine treatment will also be identical with that of acute cystitis (see p. 240).

Nephritis of Pregnancy.—This condition appears to be almost invariably due to the *B. coli*. Constipation appears to be a strongly predisposing factor, infection probably taking place from the colon via the lymphatics. Hicks¹ divides up these cases from the clinical aspect as follows: (1) Mild cases in which rest in bed, a milk diet, careful regulation of the bowels, and the administration of potassium iodide and urotropin, will probably suffice; (2) moderate cases, in which the same treatment should be adopted plus a vaccine of *B. coli*; (3) severe, in which, when combined treatment fails, evacuation of the uterus becomes necessary.

Sir Thomas Oliver² mentions four cases of pyelonephritis in women due to *B. coli*, in two of whom the pyelitis developed, not during pregnancy, but six or seven weeks after parturition, when they had practically recovered therefrom. I have myself had a similar case. Weekly injections of vaccine caused gradual disappearance of pyrexia and return to health. He concludes that 'the results achieved by vaccine therapy far outweighed anything likely to be got by internal administrations of vaccine.

Morse, while expressing his conviction of the great utility of alkalies and urotropin, says: 'In the more intense and persistent cases vaccines are the only hope.' Like myself, he holds that the vaccine should be given in the largest possible dose that will not produce a marked reaction. He would have these repeated every four days. In the case of mine above referred to the patient had a

¹ *British Medical Journal*, 1909, vol. i., p. 203.

² *Lancet*, September 25, 1909, p. 910.

normal confinement, and all appeared to go well for several weeks, except that the patient regained no strength. She then had to return to bed, and when I saw her looked very ill and weak. The pulse was about 100, and very weak; the temperature rose regularly to about 100° F. every evening. There was not much pus or albumin in the urine; *B. coli* and a Gram-positive diplococcus, probably pneumococcus, were present in fair numbers. The abdomen was lax, the uterine involuted well, and there was no pain, tenderness, nor swelling to be detected. Autogenous vaccines were prepared, and treatment begun with 50,000,000 *B. coli* and 25,000,000 (?) pneumococci. It was steadily pushed at intervals of seven or eight days without any influence whatever on the clinical condition. No reaction was produced in the slightest degree till 500,000,000 *B. coli* and 250,000,000 pneumococci were administered. There was then a slight reaction, and the condition began to improve. After several of these doses the patient was able to get up and go away for a change. She returned much better, but still rather delicate, though all signs of infection had disappeared. About a year later I was again called in to see her. She had missed a period, and there was a question of pregnancy. The pyelitis had returned. The bacteriology was as before, and treatment with the vaccine was resumed with an initial dose of 100,000,000 *B. coli* and 50,000,000 pneumococci. A month later her doctor reported as follows: For several days the patient became considerably worse, the temperature falling to below 96° F. in the morning, and rising to nearly 103° F. in the afternoon. After ten days I gave another injection of 250,000,000 *B. coli* and 125,000,000 pneumococci. On this occasion, instead of the temperature rising a

degree, as always before when a reaction was obtained, it immediately fell, and kept steady between 97° to 99° F. for a week, when it again began to rise. I then gave another injection, when the temperature rose a degree, and then again fell. She remains very thin and weak. Two months later he reported as follows : 'I am sorry to say Mrs. K.'s progress has not been very satisfactory ; for a time she improves, but only for a few days, then the temperature goes up again to about 103° F. at 6 p.m. She remains very weak.' A re-examination of the urine showed only a few streptococci and diphtheroid bacilli, very little albumin, and no pus cells. I accordingly prepared a fresh vaccine of these organisms and advised the doctor to inoculate more frequently, and endeavour to anticipate the rises of temperature, and hope ultimately to get a good result.

The general experience would therefore seem to be that cases in which the pyelitis develops some weeks after parturition are of grave prognosis, and that in vaccine treatment plus careful medical attention and nursing, good food and fresh air, the only good chance of success would seem to lie.

Acute Nephritis in Children is by no means easy of differentiation from simple cystitis. The classical signs of pus in an acid urine, high remittent temperature, rigors, and more or less serious general disturbance, are not always present, nor do they appear necessarily to be confined to the former as distinguished from the latter condition. The bacteriology has been imperfectly worked out, and I am by no means satisfied that it is always due to the *B. coli*. Urotropin is said to be useless, and full doses of potassium citrate almost specific.

Vaccine treatment on quite insufficient evidence was

not approved of at the meeting of the British Medical Association in 1910. From general experience of vaccine treatment in cases of high fever I am inclined to think that an autogenous vaccine of the *B. coli* in 2,500,000 to 5,000,000 dosages according to age could hardly fail to influence favourably such cases as were not making speedy response to ordinary treatment, and certainly could be productive of no harm.

ACUTE CYSTITIS.

Bacteriology.—The commonest cause is undoubtedly the *B. coli* group. Almost any of the ordinary pathogenic organisms may, however, be responsible, and are quite frequently encountered as allied invaders with the *B. coli*.

Preliminary Considerations.—These are of considerable importance in this affection. A predisposing factor is almost invariably present, and attention to this is almost essential to a speedy cure, and is quite essential if subsequent immunity from relapse is to be enjoyed. Such conditions as a urethral stricture, an enlarged prostate, or a vesical calculus, should be remedied as soon as the condition of the patient, general and bacteriological, will permit surgical interference. It is also very important to remember that a perhaps by no means inconsiderable percentage are really secondary to a tuberculous infection, not necessarily of the bladder, but of some other portion of the genito-urinary tract, and that the mere failure to detect tubercle bacilli in the urine does not suffice to negative this possibility. If vaccine treatment is to receive a fair chance, care should also be taken to prevent the collection of residual urine in the bladder. Urinary antiseptics should be employed, and full doses of potassium citrate administered. In this connection it

may be mentioned that the view is held by some that urotropin and alkalies should not be given together. Personally, I am by no means convinced that this is correct. The liberation of the formaldehyde from the urotropin appears to take place in the blood or kidney tubules just the same. Infection may arise either via the urethra, when an acute or subacute urethritis is usually the predisposing factor, or via the gastro-intestinal tract, which is probably much the commoner way. Chronic constipation or diarrhœa renders the intestinal wall pervious, and the bacteria are carried thence either by the lymphatics or blood-stream. Considerable attention should therefore always be paid to the state of the intestinal tract.

Vaccine Treatment.—As we have seen, the bacteriology of the condition may be quite a complex one. Great care is therefore necessary in its determination, and inasmuch as aberrant types of the *B. coli* are very common, an autogenous vaccine is likely to possess decided advantages over stock ones. At the same time, the latter are by no means as useless as is often stated. If the results of treatment are satisfactory up to a certain point, and failure to make further improvement is noted, despite increased dosage, it is well to remember that in this class of infection especially do the bacteria appear to possess the power of rendering themselves immune to the antibodies, and that this difficulty may frequently be overcome by the preparation of a fresh vaccine. In the determination of the initial dosage, consideration must be paid to the general condition of the patient, and the possible presence of other infected foci—for instance, in the prostate—in which case a smaller dosage is advisable, as thereby a threatened abscess formation may be obvi-

ated. Appropriate amounts will therefore lie between the following limits: *B. coli*, *B. proteus*, and *B. pyocyaneus*, 10,000,000 to 25,000,000; bacillus of Friedländer, streptococcus, and pneumococcus, 20,000,000 to 50,000,000; staphylococcus and *B. influenzae*, 50,000,000 to 100,000,000. The clinical signs and symptoms will indicate the necessity of repetition or increased dosage. Intervals of between three and seven days may be suitable. Treatment may have to be prolonged over many months, and, as already stated, a fresh vaccine every three months may prove a distinct advantage.

The results achieved by this therapy have varied with different observers. Success is probably in direct ratio to the attention bestowed on all predisposing and secondary factors. Most have met with more successes than failures, but there seems little doubt that in a certain percentage of cases it is impossible to secure the complete disappearance of the bacilluria. Billings¹ concludes that improvement may be brought about in all cases with vaccines alone, but where there is obstruction to the urinary flow entire recovery will usually not occur until this is relieved.

Emery² gives as his experience: 'Vaccine treatment cures all the symptoms, and reduces the pus and bacilli present in the urine to a small fraction of its original amount, but fails to remove them entirely. There is no doubt that the treatment is the best available.'

The best recorded results are those of Wulff,³ who claims to have cured eighteen cases out of twenty-one, the other three not being much benefited.

¹ *American Journal of Medical Sciences*, May, 1910, p. 625.

² 'Immunity and Specific Therapy,' p. 394.

³ *Presse Médicale*, 1910, p. 97.

Morse believes that vaccines hold out the only hope of cure, and, like myself, believes in doses of such magnitude being employed as will produce a definite constitutional reaction. In this connection I would like to point out, however, that a marked reaction, such as rigors and vomiting, may be produced even by the smallest doses. Long ago I concluded that this always meant pus under pressure, and further experience has confirmed this view. In one instance I got such a reaction with a dose of 25,000,000 after the patient had already borne several inoculations well. Mr. John Pardoe was the surgeon in charge, and on my statement that this was absolutely diagnostic of pus under pressure, he made three very careful examinations, but failed to find the focus. A few days later there was a sudden gush of 2 to 3 ounces of foul pus on catheterization to draw off the urine, the patient having all through been unable to void it for himself. Mr. Pardoe concluded that this must have come from between the layers of the triangular ligament. If this fact be borne in mind, the patient may often be saved much needless suffering.

ACUTE AND CHRONIC URETHRITIS.

Bacteriology.—The view that practically all cases of urethritis, acute and chronic, are primarily gonococcal in origin is being more and more abandoned by those whose experience of the bacteriology of this condition is extensive. Mr. Wyndham Powell, whose experience is perhaps unequalled, tells me that since he adopted bacteriological examination as a routine practice he has been much surprised to learn how numerous are the cases of acute urethritis in which the causal agent is other than

the gonococcus. Age is an important factor, and he considers that the following rough statement is not far from the truth : In cases under twenty-five years of age, 90 per cent. are gonococcal ; in cases from twenty-five to forty years of age, 75 per cent. are gonococcal ; in cases over forty years of age, only about 50 per cent. are gonococcal.

From this we see how ill-advised it is to neglect a proper bacteriological examination of all cases of urethritis, and to this cause may undoubtedly be attributed a certain percentage of the cases of failure to influence the acute condition favourably by means of gonococcal vaccine.

When an acute attack is superimposed upon a chronic gleet, the bacteriology may become complicated, and in chronic gleet it is usually very complex indeed.

Persistence of a gonococcal infection of the urethral mucous membrane is quite rare after a more or less undetermined period, the gonococci appearing to die off, either from exhaustion of food-supply or the establishment of high local immunity. If they maintain a footing at all, this they do especially in the various crypts and sinuses, as in Littre's glands and the sinuses of Morgagni, in the seminal vesicles, or in the prostate. From these their exit is usually blocked by a plug of mucus or contraction of fibrous tissue. The catarrhal condition of the urethra is then maintained by a great variety of bacteria, such as staphylococcus, streptococcus, *M. catarrhalis*, *B. proteus*, *B. coli*, *B. influenzae*, or bacillus of Friedländer.

That the gonococcus does become encapsulated in this way is certain. Thus, I remember one patient who had an acute discharge in which gonococci alone were present in great numbers every time he had a connection. Be-

tween these the discharge would perhaps entirely disappear, and after six months' abstinence he would regard himself as cured, only, as he thought, to fall a victim to fresh infection at the very next connection; whereas he was in reality reinfesting himself, as was shown by the fact that two or three doses of vaccine cured him completely and permanently. None the less, I am convinced that far too much importance is attached to the possibility of a long-continued infection, and think it relatively rare for gonococci to persist anywhere in the tissues of the genito-urinary tract for a longer period than three years.

The procedure in determining the nature of the infection should be somewhat as follows :

1. In acute attacks, cleanse the external meatus with sterile salt solution, wipe away any pus that has collected there; then gently pass the hand along the course of the urethra, discard the first bead that is expressed, and collect subsequent beads for direct and cultural examination.

2. In subacute attacks, follow the same procedure, but in addition allow the patient to micturate; then flush out the anterior urethra with plenty of sterile water, gently massage the prostate and vesicles, and collect the expressed secretion for examination.

3. In chronic cases, do as in (1) and (2); then again wash out the anterior urethra, pass a Powell's urethroscope, examine the crypts and lacunæ thoroughly, and if these are inflamed take a number of cultures from them through the urethroscope.

The specimens thus secured should be examined in stained films, and plate cultivations made in blood-agar, which should be examined after one, two, and three days.

In this way the true bacteriological condition will be determined, and the rôle of the various invaders esti-

mated, mere surface parasites being differentiated from those organisms which are involving the tissues. The desired autogenous vaccines may be prepared without difficulty from the blood-agar cultures.

Preliminary Considerations.—As vaccine treatment consists, not in the mere inoculation of the vaccine, but in the application of all such measures as will bring the antibodies to the foci of infection, and aid in the elimination of the bacteria and their products, it follows that such other special forms of treatment as experience has shown to be advisable must be applied if injections are to prove of service. Thus, in acute attacks the advent of secondary infections should be obviated as much as possible by keeping the penis in a bag of antiseptic gauze. The urethra should be kept well flushed by increasing the secretion of urine by means of suitable diuretics. Alkalies may be given if thought advisable, and oleo-resins or antiseptics by the mouth may aid in diminishing pain and swelling, and perhaps in preventing backward extension. In chronic infections careful dilatation by means of Kaulhmann's dilator will almost certainly prove essential to the liberation of the cocci from their hiding-place, and their removal by suitable antiseptic douches. It should be remembered in this connection that dilatation results in the production of auto-inoculations. The topical application of antiseptics, limited strictly to areas of inflammation, may also be advisable. It is quite outside the scope of this work to go into the surgical treatment of urethritis, but enough has been said to indicate the necessity of treating every case according to the precise clinical condition present.

Vaccine Treatment.—In gonococcal infections a stock polyvalent vaccine of proved immunizing powers may

prove even more efficient than an autogenous one, especially if the latter has to be prepared from a strain which has required repeated subculturing to obtain in a state of purity, or from one which has lost its virulence from long residence in the infected foci. In cases of early acute urethritis there is rarely much difficulty in preparing the autogenous vaccine, but this does not appear often to possess advantages over a good stock vaccine. When other bacteria are responsible for the condition, it is, perhaps, best always to use the autogenous vaccine or vaccines, as the preparation will often involve less labour than will the precise identification of the invaders.

The dosage of the vaccine to be used is a most important point, and one about which extraordinary bigotry has been exhibited. No consistently good reports have ever reached me from the use of small doses of a gonococcal vaccine, whereas full doses rarely fail to produce a good result. Despite this, numerous workers are deterred from the use of adequate doses by the reports of two or three cases in which an epididymitis or a prostatitis followed very soon after the administration of a fair dose of vaccine. Surely the complications of urethritis are frequent enough when treated on purely orthodox lines to make any thinking person pause before ascribing the advent of the complication to the administration of the vaccine. It is equally open for the vaccine therapist to retort that in default of the inoculation the extension might have been more acute and more widely disseminated. It is, perhaps, not a correct attitude of mind, but as I believe I was the first worker on vaccine treatment as applied to acute gonorrhœa, I cannot help feeling some resentment whenever I read the conclusions of those who

perchance never used a larger dose than 5,000,000 that vaccine treatment is without effect on the course of an acute urethritis. Inasmuch as the essence of all vaccine treatment is to use such doses as will produce local changes at infected foci, it necessarily follows that such observers were either working with an inert vaccine, or were employing totally inadequate dosages. An extensive experience of the subject enables me to say that I have never yet seen a dose of 25,000,000 to 50,000,000 of gonococcal vaccine have any ill effect on the course of an uncomplicated urethritis, and I have very often seen it exert a marked influence for good. When such complications as a prostatitis or orchitis already exist, it is wise to diminish the dose to one of 25,000,000, lest perchance a too large dosage may result in the production of an abscess; whereas a smaller dosage may well bring about its abortion, precisely as is seen in staphylococcal boils. If, on the other hand, a vaccine of such immunizing power is obtainable that doses of 5,000,000 to 20,000,000 do exert a definite favourable influence on the course of the infection, it is unnecessary and even inadvisable to employ higher dosages, the one thing to be borne then in mind being that, if in a certain individual the stereotyped dosage prove ineffective, recourse should at once be made to such higher dosages as will secure the desired immunizing response.

Within twenty-four hours of an inoculation there should be slight increase of the secretion, and perhaps a little constitutional disturbance and feeling of warmth in the urethra. These should speedily subside, local pain and tenderness should be lessened, the discharge should become more purulent, and phagocytosis should be seen to be active in stained films of the secretion. The in-

tervals may vary between three and seven days, as indicated by the local and general conditions.

Vaccine treatment may be begun at any time; the earlier in the course of the disease the better. It should be continued for at least three or four weeks after the complete disappearance of all indications of infection, and it is well to raise the ultimate dosage to 250,000,000 to 500,000,000, as thereby the complete extinction of the bacilli at all infected foci is rendered the more likely.

The beneficial results of vaccine treatment are to be seen, not so much in any marked shortening of the period of active symptoms, but in—(1) a diminished incidence of acute complications; (2) the almost complete obviation of the case drifting into one of chronic gleet, or presenting such after-indications of latent infection as acute or subacute arthritis, or iritis of doubtful origin; (3) the greater comfort that is secured the patient; (4) a marked influence for good on such complications as orchitis and epididymitis.

Aronstam¹ treated fifty-four cases with stock vaccines, and no local applications. The average duration of treatment was only three weeks. Three to eight injections were required to effect a cure. He concludes that recovery from acute gonorrhœa may be brought about in four weeks without injections or irrigation, and that vaccines also act well in epididymitis and prostatitis.

Frost² gives a good summary of the results obtained by various observers, and also an interesting account of a number of cases of his own. Like myself, he finds that relapses are below the average, and more quickly amenable to treatment, and that 'too small a dose is to be

¹ *Journal of American Medical Association*, 1908, p. 1419.

² *Journal of Royal Army Medical Corps*, September, 1912.

avoided, for it would appear that immunity against the vaccine is the only result.'

Menzler¹ advocates the treatment of all cases of gonorrhœa by means of vaccine. After referring to the unsatisfactory results obtained by the usual methods of treatment, he states that an injection will cause a reaction if there is any latent nest of gonococci in any part of the body, and disagrees with Bruck's view that a gonococcal infection of the urethral mucous membrane is not influenced by an injection of gonococcal vaccine. His procedure is to prescribe absolute rest in bed for two or three weeks without any urethral medication, then to begin treatment with 5,000,000 doses of vaccine, and repeat these every third or fourth day. He finds that each injection for the first two weeks is followed by an increase in the amount of discharge and of the turbidity of the urine, but that after twenty-five to thirty days this reaction is no longer produced. The average duration of treatment in twelve cases, some of which had complications, was forty-seven days. This is about the average time taken for recovery under skilled surgical treatment, so that his judgment of the good result must be founded on the manner and completeness of the recovery rather than on the time it takes.

Emery, Eyre, Hecht and Klausner,² and others, are entirely in favour of the treatment; others are equally insistent that it is valueless. In no other affection, except, perhaps, lupus, do such totally antagonistic views prevail. A possible explanation has been already offered, and the best advice, perhaps, which can be given is this: 'Begin, if you will, with small doses, even 5,000,000,

¹ *Münch. Med. Woch.*, No. 46, 1911.

² *Berliner Klin. Woch.*, No. 20, 1911.

repeated at intervals of three or four days; but if no reaction, local or general, is obtained, advance steadily to doses of 10,000,000, 25,000,000, 50,000,000, and even 100,000,000, employing a rather longer interval with the higher dosages. When a response is obtained, no further increase of dosage is for the time being advisable.'

CHRONIC URETHRITIS.

Just as there is a great difference of opinion about the utility of vaccine treatment in the acute form, so there is remarkable unanimity about its advantages in the chronic form; the only real difference of opinion is concerning the magnitude of the initial dose and interval.

The preliminary considerations which must be borne in mind in approaching a case of chronic urethritis have been already referred to. It is little use attempting to influence a chronic infection by the staphylococcus or bacillus of Friedländer with a gonococcic vaccine. The bacteriology has to be well studied, and choice made of suitable vaccines to deal with the secondary invaders, which may perchance have entirely supplanted the original inhabitant, the gonococcus. Methods for determining whether the gonococcal infection is still existent or not have been already fully discussed in previous chapters. If there be any doubt about this matter, the combined administration of a stock gonococcal and of the appropriate autogenous vaccine or vaccines is probably the safest and best procedure.

Most observers agree in fixing the appropriate initial dosage of the gonococcal vaccine at 50,000,000. Those for the other organisms may be as follows: *Streptococcus*, 25,000,000; *B. coli*, *B. proteus*, 25,000,000 to 50,000,000; *M. catarrhalis*, bacillus of Friedländer, 50,000,000;

B. influenzae or staphylococcus, 100,000,000. The intervals may vary from about five to seven days for the initial low dosages to seven to ten days for the final large dosages. Treatment may have to be prolonged, and constant watch should be kept upon the bacteriological condition, for apparently fresh infection by some other extraneous organism is by no means infrequent.

Results of Treatment.—In a considerable percentage of cases the combination of expert local treatment and the administration of a vaccine or vaccines will bring about a cure ; in a certain percentage complete disappearance of all discharge cannot be secured. A slight moistness of the urethra may persist, and a small bead of glutinous secretion may appear at the external meatus in the morning. For all practical purposes these cases are cured, but there is sometimes decided difficulty in persuading patients that this is the case, and they would be much happier if this condition could be removed, even if the alternative were a urine loaded with prostatic threads. In a few cases even the combined treatment may do no more than produce an improvement. Wyndham Powell and myself treated one case together, each employing his own special devices, for over a year, and thereafter one of us (W. P.) continued intermittent treatment for several years. There was a huge external meatus, and a large flaccid urethra, in which few inflammatory foci could be detected. No gonococci could ever be found, but vast numbers of bacillus of Friedländer and *B. influenzae*, etc., were present. After long-continued treatment, the patient seemed greatly improved, and the urethra nearly dry. When I first saw him, a dozen or more drops of milky secretion could be expressed from the urethra at any time ; but about six months later he returned, with

precisely the old condition of affairs in a modified form. The after-history has been one of alternate freedom from discharge and marked relapses.

Very few inflammatory cells are ever present, and the bacteria would appear to flourish exceedingly as more or less harmless saprophytes on the surface of the partially devitalized urethral mucosa.

One thing can be safely promised in such cases, and that a matter of the highest importance—namely, that if the combined treatment be persisted in, and adequate final dosages of gonococcal vaccine result in the production of no reaction, then freedom from gonococcal infection may safely be assumed.

VULVO-VAGINITIS IN CHILDREN.

Great attention has been paid to the vaccine treatment of this condition in America, where it appears to assume a much greater importance than in this country. Butler and Long have studied the results in two series—a first of twelve, and a second of twenty-five cases.¹ In their first series they compared the results obtained by vaccine treatment in twelve cases with those obtained in twelve other cases which were treated with antiseptic douches. The inoculations were here controlled by observations of the index, repetition being carried out before the index again fell below normal. Their dosage varied from 1,000,000 to 50,000,000, 5,000,000 being that finally recommended. The comparative results were as follows: In four of the vaccine cases clinical evidence of gonorrhœa disappeared in from ten to twenty-one days, and gonococci could not be found in smears. In five cases a

¹ *Journal of American Medical Association*, 1908, p. 744; *ibid.*, p. 1301.

cessation of discharge and disappearance of the gonococci was secured after several weeks of treatment, a change from a univalent to a polyvalent vaccine being found beneficial. In the remaining three cases recurrence occurred after apparent cure, but yielded to further treatment. Thus complete cure was obtained in every instance.

In the 'irrigation' series nine were treated respectively for twenty-five, twenty-six, twenty-six, twenty-seven, twenty-nine, forty, forty-nine, sixty-three, and ninety-six days without cessation of the discharge; while in the remaining three, after treatment of thirty-one, thirty-two, and one hundred and seventy-six days respectively, a favourable result was secured. Their conclusion was that vaccine treatment appears to be far more efficient than local antiseptic treatment. This was entirely confirmed in the second series of twenty-five cases. Thirteen of these were chronic, eleven made complete recoveries in an average of thirty-nine days; the others were acute cases, and got well in an average of forty-three days.

Hamilton and Cooke¹ treated eighty-four cases. Seventy-six of these were cured, five not cured, and three could not be traced. Their results are tabulated comparatively as follows:

Method.	Cases.	Cured.	Per Cent. of Cures.	Not Cured.	Untraced.
Irrigation ..	260	158	60	53	49
Vaccine ..	84	76	90	5	3

The average duration of treatment by the irrigation method was 10·1 months; by vaccine, 1·7 months.

¹ *Journal of American Medical Association*, 1910, p. 2123.

In ten cases they tried a combination of these methods, but found no advantage whatever over the vaccine alone; in addition to which irrigation necessitates stay in hospital, and may induce masturbation, whereas vaccine treatment may be carried out at home.

Churchill and Soper¹ treated seventeen cases with vaccines for an average duration of only nineteen days, yet in ten cases they obtained cure, and in seven improvement.

The vaccine treatment of this condition would thus appear to possess overwhelming advantages over any other available method.

ENDOMETRITIS AND SALPINGITIS.

Acute endometritis and salpingitis are nearly always secondary to either one of two primary causes—viz., gonorrhœa or parturition. Gurd² made a careful study of twenty cases of salpingitis, and found that 80 per cent. were probably gonococcal in origin, secondary contamination sometimes occurring, especially by the *B. coli*.

The precautions which must be taken in securing specimens from the uterus have been already dealt with. The significance of the organisms found may occasionally need estimating by means of serum tests.

The treatment of gonococcal endometritis is similar to that of the male tract.

That of endometritis due to infection at childbirth is practically identical with that of septicæmia (see Chapter IX.).

Chronic endometritis and salpingitis may be due to a

¹ *Journal of American Medical Association*, 1908, p. 1298.

² *Journal of Medical Research*, 1910, No. 23, p. 151.

variety of organisms, mostly of low virulence, as well as to the *B. tuberculosis*. I have not come across any literature dealing specially with these conditions. The greatest difficulty will lie in the accurate determination of the infective agent or agents. The subsequent treatment should prove relatively simple. Tuttle¹ describes one case of salpingitis of gonococcal origin, and Fisher² two cases of non-gonococcal origin. In all three cases a successful result was achieved by vaccine treatment.

TUBERCULOSIS OF THE GENITO-URINARY SYSTEM.

This may be conveniently subdivided into the following varieties :

1. Genital.
2. Urinary.
3. Genito-urinary.
4. Genital or urinary, complicated by tuberculous disease elsewhere.

It may either take the form of a tuberculous ulceration of a mucous surface, as in vesical tuberculosis, or of the formation of solid caseous masses, as in tuberculosis of the kidney, testis, or epididymis. In the former condition progress is usually rapid, and secondary infections are peculiarly liable to be incurred ; in the latter forms progress may be very slow. Healing may take place in one part, and the infection break out in another, or one organ may be involved after another.

Both the vaccine treatment itself and the appraisement of its results are beset by many difficulties. For instance,

¹ *Medical Record*, 1910, p. 2052.

² *Yale Medical Journal*, 1910, p. 438.

the diagnosis is rarely established until the progress is far advanced. In such a case prompt remedial measures are necessary, and the effects of tuberculin treatment must necessarily be so slow that trial is hardly likely to be made of this remedy, whose influence may be of doubtful benefit, when by prompt excision of a tuberculous kidney or testis good chance of a completely successful result is afforded. On the other hand, when the disease is so extensive that surgical measures are out of the question, it is hardly reasonable to expect that vaccine treatment will produce any permanently good result.

None the less, there are certain classes of cases where vaccine treatment possesses advantages greater than those offered by any other form of treatment, such as in the following instances : (1) When the disease, without being very advanced, is bilateral, as in bilateral renal tuberculosis, where surgical treatment is quite impossible ; (2) in diffuse vesical tuberculosis ; (3) when the disease is so widespread and advanced that surgical measures are out of the question ; (4) when mixed infection is especially marked, and the general condition of the patient so bad that operation is fraught with special danger.

Bacteriology.—The organism most commonly concerned in mixed infection is the *B. coli*, and it is well to remember that a persistent coli-cystitis may be indicative of a primary renal tuberculosis descending the ureter. Other secondary invaders are *B. proteus*, *B. pyocyaneus*, bacillus of Friedländer, *B. acidi lactici*, staphylococcus and streptococcus. The exact nature of the infection is to be determined as already indicated.

Vaccine Treatment.—That of the secondary infection will be precisely similar to that of the corresponding variety in cases of cystitis. That directed to the cure of

the tuberculous infection is perhaps best conducted by performing in succession a series of inoculations with Old Tuberculin, T.R., and bacillary emulsion. Personally, I prefer always to use a mixture of human and bovine preparations in equal parts. The initial dose of each preparation may be 0.00001 c.c. The amount of the Old Tuberculin may be increased with each inoculation by 0.00001 c.c. until 0.0001 c.c. is reached. The next doses may then be 0.00015, 0.0002, 0.0003 c.c., and so on, until a dosage of 0.005 to 0.01 c.c. has been attained. The intervals should be from five to seven days. If intolerance is exhibited to any dosage, as shown by pyrexia, marked constitutional disturbance, and perhaps pain and swelling of the affected part, the next administration should consist of only about one-quarter the amount which produced the reaction, and thereafter increase of dosage should be made with care.

If a preliminary course of Old Tuberculin has been carried out, the administration of T.R. may be performed on precisely similar lines, but the maximum dose attained may not exceed 0.0005 to 0.001 c.c. If intolerance is shown to any dosage, a reduction must be made as before, and subsequent increases made even more slowly and gradually than in the case of the Old Tuberculin.

If no preliminary course of Old Tuberculin has been conducted, and treatment is commenced with T.R. or B.E., the procedure must be modified, each dosage being repeated several times before any increment is made, and the intervals between inoculations extended to seven to ten days.

This scheme of treatment is but a rough generalization. Each case will need treating entirely on its own merits. The prime consideration is improvement of the

clinical condition, not the attainment of high dosages of tuberculin. Some cases make steady improvement on quite small dosages, and retrogress on larger ones ; others make no progress until quite large dosages are employed. The guidance of the opsonic index is now rarely sought, reliance being placed on observations of the clinical condition of the patient, the progress of the lesion, and on the indications afforded by the urine.

Results of Vaccine Treatment.—As has been already mentioned, it is very difficult to appraise the results of vaccine treatment. Statistics are of very little use, for they afford no indication of the severity of the infection and the condition of the patient, and the personal estimate of the immunizer, who probably alone is competent to estimate the influence for good, as having had the case under constant supervision, is always regarded with considerable distrust and suspicion. The fact that genital tuberculosis is peculiarly liable to spontaneous improvement, quiescence, and exacerbation, or appearance elsewhere, does not diminish the difficulty of forming a correct judgment. Most observers will, however, agree with the following rough generalizations :

1. Preliminary treatment with tuberculin, and, if necessary, a vaccine directed against secondary infection, may greatly improve the general condition, and so fit the patient better for a severe operation.

2. That after operation a course of specific therapy seems to expedite recovery, and minimize the risk of recurrence, especially if the infection has been widespread and incompletely dealt with at operation.

3. If the disease is bilateral or so advanced as to be beyond operation, it affords the only hope of amelioration and a prolonged existence under conditions of

moderate comfort. Only very rarely will it then succeed in bringing about cure.

4. That in a certain percentage of cases where surgical interference is not possible, although the general condition of the patient is not unfavourable, vaccine treatment does bring about a cure.

The localization of the lesion is not without bearing on the result to be anticipated from vaccine treatment. The best results appear to be secured in the genital forms, cure or considerable improvement being secured in about 50 per cent. of these cases. Of the urinary forms, bladder cases seem to give better results than do renal ; but, as we have seen, early diagnosis is seldom made of the latter, and nephrectomy is, as a rule, performed, unless the disease be bilateral. In genito-urinary cases the prospect of ultimate cure is poor, but surprising amelioration is often brought about. Thus, in the case recorded on p. 239 of the Third Edition, treatment was begun when the patient was desperately ill. Vaccine treatment reduced the pus in the urine from 20 per cent. to 0·5 per cent., and the patient recovered sufficiently to lead a useful life for another two and a half years. In another case about which I have been recently consulted the condition nine months ago was beyond operation. The left testis and seminal vesicle, the prostate, bladder, and left kidney, and possibly the right, were all infected, and the urine was loaded with pus, tubercle bacilli, and *B. coli*. Nine months of Margate air and active treatment with tuberculin have led to a great increase of weight, marked improvement of the general condition, apparent arrest and retrogression of most of the lesions, the almost complete disappearance of pus and *B. coli*, and a great diminution of the tubercle bacilli in the

urine. Numerous cases similar to these two are now on record.

In the fourth of our subdivisions—viz., when tuberculous infection is present elsewhere in the system (for instance, in the lungs)—the prognosis is decidedly bad, as it is almost invariably found that if the genito-urinary condition improve, the pulmonary condition progresses, and *vice versa*.

Wildbolz¹ summarizes his observations on thirty-one renal cases treated with tuberculin as follows: A microscopic examination of the kidneys in five cases, after the prolonged administration of tuberculin according to the German procedure, failed to reveal any tendency to healing of the tuberculous process. In four of the patients the infection was unilateral, and the conditions unusually favourable for a cure, if the tuberculin had been able to effect it, but in each instance the disease progressed, and nephrectomy became necessary. On the other hand, the general health remained good, and the tuberculous process had not gone on to caseation or cavity formation, notwithstanding the long duration (eight years in one case).

He considers that tuberculin has a general favourable toxin-binding influence, but no appreciable local effect in renal tuberculosis. The general health is therefore almost invariably improved, but cure is very rarely brought about. Nevertheless, he thinks that in early cases of unilateral disease, especially in children, trial of tuberculin is fully justified, especially as thereby the constant supervision of the process enables a prompt decision to be formed as to when nephrectomy is necessary. Great caution is necessary if it be given in advanced cases, as

¹ *Berliner Klin. Woch.*, June 27, 1910.

additional toxæmia may be induced. As he rightly says, we have to be more exigent of tuberculin treatment in renal than in pulmonary tuberculosis, for nephrectomy affords a chance of actual cure which is lacking in the latter instance.

The largest recorded series of cases of tuberculous epididymitis is the fifteen cases cited by Western. Of these, six were cured in from three to nine months; four were greatly improved, the sinuses healed, and, though the disease was still evident, the patients were able to go about; four had only been under treatment less than two months, but were doing well; and one, which also suffered from diffuse pulmonary phthisis, alone derived no benefit.

The results obtained in thirty-four cases of various descriptions at St. Mary's Hospital may be thus tabulated:

Site of Infection.	Total Number.	Cured.	Much Better.	Better.	No Better or Worse.
Testes ..	9	3	2	2	2
Kidney ..	8	2	2	3	1
Bladder ..	17	2	4	8	3

The subsequent history of Western's and the St. Mary's Hospital cases would be particularly interesting. So far as a comparison can be drawn from these and Wildbolz's cases, it would seem that better results are to be anticipated from the use of tuberculin according to the English procedure than according to the German method.

CHAPTER IX

DISEASES OF THE CIRCULATORY SYSTEM, INCLUDING THE BLOOD, HEART, LYMPHATICS AND THEIR GLANDS. CEREBRO-SPINAL FEVER, AND THE ACUTE SPECIFIC FEVERS NOT ALREADY DISCUSSED

Disease.	Associated Organisms.
Septicæmia and py-æmia	<i>Streptococcus</i> , <i>pneumococcus</i> , <i>staphylococcus</i> , <i>gonococcus</i> , <i>B. coli</i> , <i>B. pyocyaneus</i> , etc.
Endocarditis ..	<i>Streptococcus</i> , <i>pneumococcus</i> , <i>B. influenzae</i> , <i>gonococcus</i> , <i>B. tuberculosis</i> .
Pernicious anæmia and scurvy	Doubtful; possibly <i>streptococcus</i> .
Adenitis and lymphangitis	<i>Streptococcus</i> , <i>staphylococcus</i> , <i>pneumococcus</i> , etc., and the <i>B. tuberculosis</i> .
Cerebro-spinal meningitis	<i>Meningococcus</i> , <i>pneumococcus</i> , <i>streptococcus</i> , <i>B. coli</i> , <i>B. typhosus</i> , <i>leptothrix</i> , <i>B. influenzae</i> and the <i>B. tuberculosis</i> .
Acute rheumatic fever and its complications	<i>Streptococcus rheumaticus</i> .
Malta fever	<i>M. melitensis</i> .
Plague	<i>B. pestis</i> .
Scarlet fever	<i>Streptococcus conglomeratus</i> .
Hydrophobia, or rabies	Unknown.
Sleeping sickness ..	<i>Trypanosoma Leishmanii</i> .

SEPTICÆMIA AND PYÆMIA.

Preliminary Considerations.—If by the term ‘septicæmia’ we mean the mere presence of bacteria in the blood, then very many infectious diseases fall into this category during some period of their course. Thus,

in enteric fever, influenza, pneumonia, and pulmonary tuberculosis, the organisms gain entry into the general circulation. They do not, however, appear as a rule to multiply there, nor is their presence constant throughout the whole course of the disease. The designation 'septicæmia' is, in its strict application, reserved for the description of those conditions characterized by the multiplication of the bacteria in the blood-stream, but is commonly extended to those conditions in which bacteria can be isolated from the blood, or in which evidence of their presence is given by the formation of pyæmic abscesses. In some instances a primary focus of infection is easily discoverable, as in the case of the uterus in puerperal septicæmia. In other instances the primary focus is not discoverable, although it doubtless has, or had, existence.

When the original focus of infection can be found, whether in the ears, uterus or its appendages, abdomen or urethra, it is obvious that it must receive prompt and thorough attention if the secondary septicæmia is to be dealt with successfully.

During the period between the taking of cultures and the first inoculation, the temperature chart should be carefully taken and the clinical changes duly noted. As to the precise time at which the first inoculation should be given, opinions slightly vary. Personally, I think as soon as possible, no matter what course the temperature is then taking. Wynn says it should be only given on a falling temperature. Theoretically, there is some justification for his view, for an inoculation always tends to raise the temperature; and if an additional impetus be given to a rising temperature, it is conceivable that a point might be reached which is not

desirable. In practice I have, however, never encountered any such ill effect. Within eighteen to twenty-four hours of such inoculation, if an immunizing response has been obtained, it should be evidenced by a steadying of the temperature, the reduction of its highest level by at least 1° , improvement of the pulse and respiration, and, above all, by marked change for the better in the patient's subjective symptoms. The exceedingly toxic and anxious expression should be replaced by a healthier and calmer look, and a desire for sleep should be evinced. Change in any one of these directions is a hopeful sign, but the more that enter into the combination the better the result has been.

If no definite response is secured in any of these directions within twenty-four, or at the most, thirty hours, reinoculation is advisable. In view of the possibility that the reaction may have been unduly delayed, and in view of the fact that one inoculation may result in raising the sensitiveness of the tissues, it is unwise ever to increase the dosage at the second administration—the former one should be repeated; but in the event of a second failure to secure response in thirty hours, a double dosage should be then employed. If, on the other hand, the desired reaction is obtained on the first occasion, I think the best procedure is to wait till no further improvement, or even a slight retrogression, is taking place, and then to repeat the former dosage. In practice this interval works out to between two and five days, and usually to between forty-eight and seventy-two hours.

As the patient progresses to recovery, the dosage may be increased, and the intervals prolonged usually with advantage to the patient.

The preliminary or simultaneous administration of antistreptococcal serum from the objective of neutralization of circulating toxin is to be condemned. This serum, so far from possessing antitoxic properties, is sometimes highly toxic; its only influence is antibacterial. The use of typhoid anti-endotoxic serum and of Flexner's anti-meningococcal serum rests on a much sounder basis. These do contain antitoxins beyond doubt, and some recently prepared antistaphylococcal and antipneumococcal sera may possibly likewise do so. The objections to the use of vaccines in septicæmic conditions almost entirely rest on misapprehensions and ignorance both of their properties and of the processes of immunity. Only quite exceptionally do vaccines contain any appreciable amount of toxin; usually they contain no free toxin whatever. The local introduction of a very small amount of toxin into healthy tissues cannot exercise any effect upon the amount of toxin in circulation. It may directly excite the formation of antitoxin, but this also to a negligible amount. What it does do is to excite locally the formation of antibacterial bodies—agglutinin, lysin, and opsonin—and the only way in which harm can result is from the formation of such excess of lysin that the bacteria are directly dissolved in the blood-stream instead of within the cells, and that thereby the amount of circulating toxin may be increased to the detriment of the patient. In practice the main response is by the increased elaboration of opsonin. This, by stimulating the phagocytosis of the bacteria and the consequent destruction of their toxins within the leucocytes, more than counterbalances any possible increased lysis of the bacteria in the blood-stream. Another misapprehension which needs correction is that the presence of bacteria

in the blood-stream is capable of inciting the formation of antibodies. Antibodies are not formed in the general circulation, but in the blood-forming organs, muscles, and subcutaneous tissues. It therefore follows that it is only when the circulating bacteria have been trapped in such localities that any stimulus is given to the formation of antibodies. The introduction of a small dose of dead bacteria into healthy tissues is a convenient way of giving this stimulus quickly and to an adequate degree. Toxin elimination is to be assisted in every possible way, such as by the skin, kidneys, and bowels. Plenty of water should be given by the mouth, and high enemata of salt and water may prove very helpful.

Bacteriology.—This is, as a rule, easily determined by means of blood-cultures (for technique see p. 86); but it should not be forgotten that incubation may sometimes have to be continued for two or three days, and that cultivations may have to be taken on more than one occasion if the organisms are few in number. If failure be still experienced, cultivations of the urine will often give the desired information.

Vaccine Treatment—Control of Dosage and Intervals.—There are still some who persist that dosage and intervals should be controlled by observations of the opsonic index. To this procedure there are several objections: Firstly, the content of the blood in immune bodies alters with such great rapidity in these conditions, that by the time that the estimation has been completed, a totally different content may exist. It is therefore impossible ever to estimate even approximately what is the blood condition at the same time as inoculation is performed. Secondly, that if the attempt is to be made to make even such a rough estimate, observations of the index

must be made at very frequent intervals, even every two or three hours ; and thirdly, that, although, as we shall see later, the leucocytes often possess greatly diminished powers both of leucocytosis and of the subsequent digestion of the bacilli in the determination of the opsonic index, no account is taken of this variation.

Most observers on these theoretical grounds, as well as from the results of practical observation, have discarded 'indical' control, and have substituted other means of guidance for dosage and intervals. The conclusion of those who have had the widest experience is that a carefully kept four-hourly chart, combined with observations of the pulse, respirations, various other symptoms, and especially the general condition of the patient, afford ample guidance of the progress of immunization. Personally, I have not yet lost a single case of septicæmia, although called in in several instances as absolutely a final hope, and regard this class of case as the most easily managed in the whole domain of bacterial diseases, and as the one above all in which hope should never be abandoned, so long as the patient is alive. My rule is to work day and night till the autogenous vaccine has been prepared. This may be easily done in eighteen to twenty-four hours, where material can be obtained from a pyæmic abscess, or from an infected uterus.¹ When blood-cultures alone are available, twenty-four to forty-eight hours may be occupied over the task ; but twenty-four to thirty hours usually suffice. Heating for forty-five to sixty minutes at 60° C., and the addition of 0·5 carbolic acid or of 0·3 tricresol, is ample to secure

¹ Western (Proceedings of the Royal Society of Medicine, March, 1912, Obstetrical Section, p. 214) describes thoroughly the way in which cultures should be taken from the uterus.

sterility, or the destruction of all but a very few individuals whose vitality is so impaired that multiplication in the tissues is impossible. Wynn, Western, and myself have made tens of thousands of inoculations between us with vaccines prepared in this way, without encountering a single abscess as the result, and it is quite time, in the interest of patients, that academic objections on the score of possibly incomplete sterility of the vaccine should be finally dropped. As soon as possible after the vaccine is ready it should be used for inoculation. The initial dosage will vary slightly with circumstances. The more serious the condition the smaller the dose ; but if immunizing effects are to be produced, it is very ill-advised to employ too small doses. The following dosages within my experience and that of others are advisable : *Streptococcus*, pneumococcus, gonococcus, *B. coli*, 10,000,000 to 25,000,000 ; *B. influenzae*, *B. typhosus*, *B. pyocyaneus*, staphylococcus, pneumococcus, and *M. melitensis*, 25,000,000 to 50,000,000.

Results of Vaccine Treatment.—Personally, I do not believe that bacteria circulating or even multiplying in the blood and the blood alone are capable of killing a patient. Death takes place from toxic absorption from a localized focus or foci of infection, whether in the lung, heart, uterus, or peritoneum. It therefore follows that, on the possibility of dealing adequately with these foci, of limiting further toxin absorption, and of facilitating the elimination of what toxin has been already absorbed, lies the essential to a successful issue, and the success that attends on vaccine treatment is in direct ratio to the aid it renders to these processes. In ulcerative endocarditis the local lesion is not accessible ; failure in vaccine treatment is therefore the rule. In endometritis and salpingitis complete access is not always obtainable ; success is

therefore modified. In general septicæmia due to wounds, an infected prostate, urethra, appendix, or joint, full access is obtainable, and success should always attend the combined method of treatment, provided only that the toxæmia is not so far advanced as to make recovery therefrom impossible.

One of the best accounts of the treatment of septicæmia by means of vaccines that has appeared is that of thirteen cases by Wynn.¹ His results may be tabulated as follows :

Nature of Infection.	Highest Tempera- ture.	Result.
Enteric with <i>B. coli</i> septi- cæmia.	106 °F.	Complete defervescence in fifteen days.
Puerperal streptococcus and <i>B. coli</i> .	101·2	Complete defervescence in six days.
Puerperal streptococcus and <i>B. coli</i> .	104	Complete defervescence in thirty days.
Puerperal streptococcus and <i>B. coli</i> .	104	Complete defervescence in thirteen days.
Puerperal streptococcus and <i>B. coli</i> .	106·8	Death in sixteen days.
Puerperal streptococcus and <i>B. coli</i> .	103	Defervescence in eight days.
<i>B. coli</i> septicæmia.	104	Speedy recovery.
Septicæmia and pyæmic pneumonia.	104·6	Complete defervescence in eleven days.
Cellulitis septicæmia.	105	Complete defervescence in eleven days.
Septicæmia after nasal re- section.	105	Complete defervescence in twelve days.
Septicæmia, pyæmia, and pyelitis.	104·8	Septicæmia cured in about eight weeks.
Gonococcal septicæmia.	102	Cure in about three weeks.
Gonococcal septicæmia.	104·8	Hopeless from the begin- ning ; death.

In addition to the above, Wynn treated eight other cases of puerperal septicæmia, making thirteen in all,

¹ *Journal of Vaccine Therapy*, vol. i., No. 9, p. 239.

with only two deaths. Of these five were mild, the temperature not rising above 102° F., and all recovered. The other eight were severe, and in six of these streptococci were recovered from the blood. Of these six five recovered. The other fatal case was not seen by Wynn, he only prepared the vaccine. These two fatal cases were the only ones in which the uterus was curetted; all the others received douches. The type of streptococcus was as follows: In two, *pyogenes longus*; in three, *salivarius*; in eight, *fæcalis*. The original paper is well worth consulting. Wynn's conclusions are 'that vaccines may be depended upon to give considerable help in cases of septicæmia, that the recorded cases were all of great severity, and that a much greater mortality might reasonably have been expected.' He found an alteration in the type of temperature after the first or second dose. When previously remittent or sustained at a high level, it became intermittent, and associated with this change in temperature subcutaneous abscesses were often noticed to appear with great suddenness. These might subside without suppuration, and are to be regarded as evidence of an attempt to localize the infection.

Hartwell¹ treated eighteen cases of what he describes as puerperal septicæmia; but inasmuch as blood-cultures were made in only four cases, and in two of these growth was not obtained, it is impossible to say how many of these were truly septicæmias. None the less, the fact that all made good recoveries in response to vaccine treatment, even when serum injections and other measures appeared about to fail, must be taken as some evidence that definite good accrued. In some of the cases it was noticed that the response was delayed. In these a

¹ *Surgery, Gynaecology, and Obstetrics*, September, 1909, p. 271.

discharge of pus, probably from the tubes, was the signal for improvement to begin.

Western¹ records the results obtained in 100 cases of puerperal sepsis at the London Hospital: 56 of these were treated with vaccines, 44 according to other lines. Of the 56 vaccine-treated cases 38 recovered, the mortality being 32 per cent. Of the other 44, 20 recovered, the mortality being 55 per cent. While some of these latter cases were untreated because death occurred before any specific treatment could be applied, so many of them were comparatively mild cases, that the bias is towards a lowering of the mortality rate among the uninoculated, owing to an excess of mild cases.

Of the 56 treated cases 28 gave definite evidence of bacteria in the blood, either by yielding positive blood-cultures, or by the production of pyæmic abscesses. In these the mortality rate was only 52 per cent., despite the inclusion in the list of six cases which only received one dose of vaccine without twenty-four hours of death. Among the untreated cases, 16 fall into this category of true septicæmias. The mortality among these was 87·5 per cent.

Western's conclusions, as founded on what he regards as a number of cases too small to enable a final judgment to be pronounced, is that the mortality among cases of true septicæmia may be reduced by inoculation with appropriate vaccines by about 33 per cent.

The bearing of the nature of the infecting agent upon the prognosis is somewhat as follows: Streptococcal cases offer the worst prognosis, especially if *B. coli* be also present. Next *B. coli* plus pneumococcus, then *B. coli* alone; while uncomplicated infections by the staphylococcus offer much the best prognosis.

¹ *Loc. cit.*

As regards septicæmias due to other than uterine infection, many cases are now on record. For instance, included in Wynn's list are eight cases of this kind, all of which recovered. I have myself had a similar number, in most of which the prognosis was very grave, yet all made good and quick recoveries.¹ Numerous other cases, either singly or in small groups, have been described by various observers; and while it must be admitted that successes are much more likely to be recorded than failures, I think enough evidence has been here offered to justify the conclusion that vaccine treatment affords by far the best hopes of recovery in cases of septicæmia.

ENDOCARDITIS.

Preliminary Considerations.—When we consider that the bacteriology of endocarditis is precisely the same in many instances as that of septicæmia, and that, indeed, the condition must have been a septicæmic one at the beginning, it would seem justifiable to expect that equally good results should likewise be secured from vaccine treatment. This, however, by no means is the case, and it is necessary to look round for some explanation of the fact. One factor has been already mentioned—viz., the existence of a focal infection which cannot be dealt with surgically. Although these foci are immersed in a bath of blood, the actual blood-supply to the part is very deficient from the point of view of overcoming a bacterial infection. The researches of Rosenow² into the blood condition in this disease throw considerable light on the question. He finds that the bacteria, in

¹ For two of these see *Lancet*, September 11, 1909, p. 780.

² *Journal of the American Medical Association*, November 12, 1910.

course of time, immunize themselves against, or adapt themselves to, the antibodies of the host, that the bacteria grow much more rapidly in the patient's serum than in a normal serum, and that when they grow in the patient's blood or 'in vitro' in his serum, they acquire a resistance to phagocytosis and to intra-leucocytic destruction. The leucocytes seem to have lost the intracellular digestive enzyme which Zinnser has shown them normally to possess. Complement is also often found to be in defect in the serum. It would thus appear that most profound changes are induced in the blood by a chronic bacterial infection thereof, which do not obtain in the case of an acute septicæmia. If these profound changes are at all advanced, it is obvious that the production of a mere increase of opsonin, lysin, etc., as brought about by inoculation with a vaccine, is hardly likely to prove effective; but that, on the other hand, if, for some reason, these changes are not far advanced, good may be expected to result even to the point of the production of a cure. It is much to be desired that a full investigation of the blood and bacteria from these aspects should be made in future in all cases of infective or ulcerative endocarditis, as the further elucidation of the conditions under which failure is experienced may, in the natural course of events, lead to the device of measures whereby these conditions may be overcome.

Bacteriology.—The commonest infective agent is undoubtedly the streptococcus; the gonococcus, staphylococcus, pneumococcus, and *B. influenza* may, however, also be responsible. Libman and Cellier found a streptococcus in thirty-five out of thirty-six cases, the other being due to the *B. influenza*. The type of the streptococcus appears to have been that described as '*mitior*'

or '*viridans*' by Schottmüller. Horder finds that it is usually of the '*fæcalis*' or '*salivarius*' type, rarely of the '*pyogenes longus*.'

Vaccine Treatment.—With the considerations already mentioned before us, it is obvious that the opsonic index is an altogether inadequate guide to the progress of immunity. The general condition of the patient and the clinical signs and symptoms may well be substituted for it.

The first case of acute infective endocarditis treated by means of a vaccine was that described by Barr, and treated by Douglas. It was a very severe case of streptococcal infection. Rigors occurred at least once in every twenty-four hours. The temperature rose to 104° to 105° F. There was pleurisy, with pleuro-pericardial friction, but no marked effusion. All the various brands of antistreptococcic serum had been tried without much benefit. The index was estimated twice daily, and injections given of 5,000,000 to 12,000,000 at each fall of index. The patient made an excellent recovery, and, except for the effects of phlebitis in the left lower limb, was soon quite well.

Latham¹ has recorded a similar case treated by the oral administration of doses of 1,000,000 cocci by the mouth. The process of immunization was exceedingly slow, but ultimately complete in twelve months.

Molyneux² has described a case in a baby aged four months, in which there was also a pyæmic abscess in the sacro-iliac joint. This was due to an infection by the *Staphylococcus albus*, and despite a very grave prog-

¹ Proceedings of the Royal Society of Medicine, October, 1910, Supplement, p. 117.

² *British Medical Journal*, 1910, ii., 1772.

nosis, recovery was brought about in three months. For the first two months 2,500,000 were given weekly; during the last month this dosage was gradually reduced, the final dose being one of only 500,000.

Thompson¹ has described his results in seven cases. Three of these were cured, and four were improved for a time, but ultimately died. He states that in no case did an autogenous vaccine fail to produce some improvement, such as fall of temperature or general well-being. They were all acute cases. Four appear to have been due to the *Staphylococcus aureus*, three to a streptococcus. Vaccines of the former were used in doses of 50,000 000 to 300,000,000 at intervals of four to six days; those of the latter in doses of 10,000,000 to 150,000,000, either every day or every other day. Two of the three streptococcal cases were ultimately fatal.

Horder² claims to have had a considerable experience of the vaccine treatment of acute and chronic infective endocarditis, and considers that the treatment, though occasionally attended by encouraging results for a time, probably never saves the patient, but that, nevertheless, in view of the futility of all other modes of dealing with these diseases, a good trial should always be made of specific inoculation. In the former publication he refers to his results in two cases due to a streptococcus and two due to the *B. influenzae*. In the former some amelioration was produced for a time, but death ultimately ensued. One of the influenzal cases appears to have been freed from the infection by the administration of four doses of 1 milligramme of the bacilli, and four doses of

¹ *American Journal of Medical Science*, 1909, p. 169.

² *Practitioner*, May, 1908, p. 714, and *Clinical Pathology*, pp. 190 and 191.

2 milligrammes given at intervals of four days. (Note 1 milligramme of dried *B. influenzae* probably contains 10,000,000,000 bacteria.) For the acute endocarditis occurring as a complication of rheumatic fever, see Acute Rheumatic Fever.

PERNICIOUS ANÆMIA AND SCURVY.

The connection between these affections and infective conditions of the gums and gastro-intestinal tract is becoming increasingly clearer; and it would appear that vaccine treatment may hold out some hope of amelioration even in the former intractable condition. If it is to prove of any material benefit, it should obviously be employed as early in the course of the disease as possible. In two or three instances treatment has been conducted with a streptococcus derived either from the gums or faeces, but inasmuch as it was begun only when the disease was far advanced, nothing more than a slight amelioration could be definitely noticed. In view of the gravity of the prognosis in the former of these conditions, I would suggest that the bacterial examination of marrow from one of the rib bones should be made, and that an operation to this end would be amply justified.

ADENITIS AND LYMPHANGITIS.

Acute.—See Abscess and Erysipelas.

Chronic.—The only form of chronic adenitis to which vaccine therapy has been extensively applied is the tuberculous form.

Bacteriology.—It is the custom to regard the infection in these cases as primarily due to the *B. tuberculosis*, and any invasion by the pyogenic cocci as secondary to

that by the *B. tuberculosis*. It is by no means certain that this is the correct view. It is equally probable that impairment of the vitality of the tissues from the attacks of the pyogenic and other bacteria is essential to enable the tubercle bacillus to gain a footing. Thus it is well recognized that carious teeth, pyorrhœa alveolaris, follicular tonsillitis, infections of the scalp, and other conditions giving rise to septic absorption, are frequently found in cases of cervical adenitis.

The type of the tubercle bacillus at work also requires consideration. This seems to vary somewhat with the locality. Combining the observations of the recent English and German commissions, we find that in 25 cases of cervical tuberculosis the human type was isolated in 16 instances or 64 per cent., and the bovine type in 9 instances or 36 per cent.; whereas in 38 cases of abdominal tuberculosis the human type was isolated in 15 instances or 39·5 per cent., and the bovine type in 23 instances or 60·5 per cent. Thus in cervical tuberculosis infection by bacilli of human origin occurs nearly twice as often as by those of bovine origin, whereas in the abdomen the reverse is the case. In other words, if the source of infection be the milk, the bacilli are twice as likely to gain ingress through the intestinal mucosa as via the tonsil. Considering all forms of glandular tuberculosis together, it appears that in about 50 per cent. of the whole the infection is by the human type, and in 50 per cent. by the bovine type.

The bearing of these facts upon the choice of the variety of tuberculin for treatment in these cases should obviously receive careful consideration, but this, unfortunately, it hardly ever receives, and I cannot but feel that it is to this neglect that a certain percentage of failures are

to be attributed. The best way of determining the precise nature of the infection would appear to be by making estimations of the opsonic index to both the human and bovine strains under varying conditions. Thus a preliminary estimation might be made: the glands massaged and re-estimation made on samples of blood taken at stated intervals (*vide* p. 64), that strain to which the greater variation was exhibited being then regarded as the true infective agent. As an alternative method, a moderate dose, say 0·0001 c.c., of mixed T.R. or B.E. may be given, and observations made daily to learn the extent of the negative and positive phases, that strain to which the most prolonged negative phase and greatest positive phase is exhibited is again to be regarded as the infecting strain. That these considerations are worthy of practical attention is shown by the observations of Stewart and Ritchie,¹ that 10 per cent. of their cases—which included other than glandular cases—refused to respond to inoculations with T.R. of human origin, and by the failure by Ritchie in eleven cases to secure absorption of tuberculo-opsonin in the serum of tuberculous cases by treatment with tubercle bacilli of human type. These diagnostic methods are troublesome and tedious, and opportunities for their performance are sometimes lacking. I therefore suggested three or four years ago that the difficulty should be overcome by using a combination of the preparations of each strain for the treatment of all cases of tuberculous adenitis. This suggestion was well received by Emery and others, and has, I know, been adopted by many. Unfortunately, the results of the procedure do not appear to have been yet recorded in the literature

¹ *Edinburgh Medical Journal*, May, 1907

Preliminary Considerations.—As we have seen that there are beyond doubt certain definite predisposing causes, especially to infection of the cervical glands, it is obviously necessary to secure the elimination of these before beginning any course of specific therapy. So also there may be predisposing causes to abdominal infection. Improper feeding and catarrh of the gastro-intestinal tract may certainly be instanced, and Arbuthnot Lane is most emphatic in his belief that too frequent feeding and constipation exercise an especially prejudicial influence. These, likewise, will therefore require rectifying in cases of abdominal adenitis.

It is also necessary to take into consideration the clinical characteristics of the lesion. If liquefaction has occurred, a course of tuberculin cannot well be expected alone to produce anything but a very slow absorption, and it becomes necessary to decide whether aspiration of the contents or an open operation should be performed. Some workers report exceedingly satisfactory results from the former procedure; others condemn it as liable to result in infection of the needle track and a consequent sinus. If destruction of the tissues of the skin is threatening, the best course undoubtedly is an immediate open operation, as thereby a better cosmetic result will almost certainly be secured. If this does not appear to be imminent, the procedure may be left to the individual preference of the medical man. Trial may first be made of aspiration, but unless a very wide needle be employed, extraction of the liquefied and caseous material may well prove exceedingly difficult.

If sinus formation has already occurred, a course of treatment directed against the allied invaders may well prove a useful preliminary to any drastic operation.

In all cases, but especially in those where caseation or fibrosis are marked features, it is even more necessary to insure that the advent of plasma, laden with its immune bodies, should be freely possible than it is to raise the amount of immune bodies in the general circulation. The way in which this is to be secured has been already fully dealt with.

Vaccine Treatment.—The most valuable account of the results obtainable from the use of human T.R. is that given in the *British Medical Journal*, August 28, 1909, as based upon 87 cases treated at St. Mary's Hospital. In 8 of these inoculation was employed merely as an adjunct to removal by operation, in every instance with satisfactory results and no recorded recurrence. In the remaining 79 cases inoculation was the chief method of treatment: 43 of these had been operated on previously with ill success; 21 of them had been operated on more than once, and 5 of them had had ten or more operations. When the glands disappeared altogether, or were reduced to a size not larger than a cherry-stone, and then remained hard, and did not vary in size, they were regarded as *cured*. When there was marked diminution, but the glands remained as large, say, as raisins, they were considered as *much better*; when the reduction was slight only, they were called *better*. The results in the 79 cases were as follows: Cured, 27; much better, 22; better, 18; unchanged, 8; worse, 4. Relapse, after some degree of improvement, occurred eleven times. Secondary infections were dealt with when necessary by means of vaccines.

In any average eight cases, therefore, in which inoculation is adopted with correct dosage, five are to be expected to show marked improvement, and of these, two or three

will be cured, two will probably improve slightly, and one or two fail. The age is a point of considerable prognostic import. The best results are to be anticipated in children under five, and in young adults from fifteen to twenty-five, after which they gradually deteriorate. The worst results are obtained in those between ten and fifteen years of age. This is shown in the following table by Carmalt Jones :

Result.	Years of Life.					
	1st	2nd	3rd	4th	5th	6th
	Five.	Five.	Five.	Five.	Five.	Five.
	Per Cent.	Per Cent.	Per Cent.	Per Cent.	Per Cent.	Per Cent.
Good	75	50	50	84	70	43
Moderate	25	44	20	0	7	43
Bad	None	6	30	16	23	14

The initial dosage recommended is 0.00001 c.e., which may be repeated at intervals of seven to ten days, and gradually increased to a maximum of about 0.0001 c.e. Treatment may have to be prolonged over six to twelve months or even longer.

CEREBRO-SPINAL MENINGITIS.

Bacteriology.—This term is taken to include not only the epidemic variety due to the meningococcus of Weichselbaum, but also the posterior basal form of Still, which may be due to an attenuated variety of that organism, and the other acute sporadic forms, and also tuberculous meningitis. The precise nature of the infective agent should always be determined by means of lumbar puncture. The other organisms, which seem capable of setting up this condition, are Still's coccus, probably only an attenuated form of the meningococcus,

the pneumococcus, streptococcus, staphylococcus, *B. coli*, *B. typhosus*, and *B. influenzae*; while a leptothrix has been found on several occasions by McDonald and Ritchie, and MacDonald,¹ and by Clarke and Williamson.²

Preliminary Considerations.—The factor which militates most against the production of good results by vaccine treatment is that in these affections there is an accumulation of fluid under pressure in the cerebro-spinal spaces, a fluid which is perhaps laden with bacteria and pus cells, but more or less completely devoid of antibodies. So long as a high hydrostatic measure is maintained, access of antibodies from the general circulation is practically impossible. The procedure which accordingly has proved most useful, is the withdrawal by means of lumbar puncture of considerable amounts of inert cerebro-spinal fluid, and its replacement by a rather smaller amount of a suitable antibacterial serum such as Jobling and Flexner's antimeningococcic serum. Variations in the severity of the disease in different places and during different epidemics makes it difficult to estimate the precise benefit derived from the use of such sera, but there appears to be little doubt but that a reduction of about 20 per cent. in mortality, a lessening in the severity of the after-effects, and a shortening of the period of convalescence, are obtained thereby. The serum should be used as early in the course of the disease as possible.

Vaccine Treatment.—This has been but seldom resorted to, and as we have seen, there are definite reasons why it is likely to prove useless. The best justification for its use is an inability to obtain a reliable serum. The

¹ *Journal of Pathology and Bacteriology*, 1909, p. 119.

² *British Medical Journal*, January 13, 1912, p. 57.

vaccine should then be given subcutaneously, and a considerable quantity of the inert and infected cerebro-spinal fluid withdrawn by lumbar puncture in the hope that the access of antibodies may thereby be facilitated. Inasmuch as rapid loss of virulence occurs in subcultures, especially of the meningococcus, a first subculture should be employed, whenever possible, for the preparation of the vaccine. Only two cases of cerebro-spinal meningitis successfully treated by means of vaccine are on record, and of the failures we do not hear, beyond the three recorded by Bosanquet and Eyre. Hector MacKenzie¹ has treated one case successfully. A first dose of 120,000,000 was followed in ten days by one of 20,000,000, in another seven days by 143,000,000, and after yet another seven days by a final dose of 71,000,000. Rundle and Mottram² have also had one successful result in a case in which the prognosis was distinctly bad. The first dose was 200,000 organisms, and in the subsequent twenty days, four doses of 500,000 were given. Each administration they found to produce a definite negative and positive phase.

In most of the forms of cerebro-spinal meningitis death takes place with such rapidity that little opportunity is afforded for vaccine treatment. Tuberculous meningitis runs a much slower course, and it is possible that vaccine treatment may here prove of some avail. This has, however, been a neglected field, and only two or three isolated cases have been recorded in which good has been found to accrue from this procedure. Thus Buchanan showed before the Liverpool Medical Institute, on December 5, 1907, a child who had suffered from

¹ *British Medical Journal*, 1907, i., p. 1408.

² *Lancet*, July 27, 1907, p. 220.

tuberculous meningitis, and recovered after an illness of four weeks with eight days' coma. The symptoms were classical: Calmette's test was positive, and the cerebro-spinal fluid contained excess of lymphocytes. After an injection of 0·000025 c.c. T.R. the child showed almost immediate improvement, and gradually regained consciousness. Three weeks later the dose was repeated. Recovery was uninterrupted, and the child was quite intelligent and able to run about. Raw¹ tried inoculations in four cases, which exhibited all the classical symptoms. In two of these tuberculin had no effect, and the children died; in the other two all the symptoms disappeared after four injections, and the children made a rapid recovery.

ACUTE RHEUMATIC FEVER AND ITS COMPLICATIONS.

Bacteriology.—The results obtained by the vaccine treatment of acute rheumatism and its various complications, such as arthritis, endocarditis, and chorea, go far to confirm the view long held by many, that the true infective agent in these conditions is the diplococcus, or *Streptococcus rheumaticus*, so fully worked out by Poynton and Paine. This organism is probably identical with a diplococcus described by Leyden in 1894, Triboulet in 1897, and Wassermann in 1899, which Triboulet regards as being identical with Thercelin's enterococcus. Poynton and Paine's organism is a very small diplococcus growing best in equal parts of a mixture of broth and milk. It has strong acid-forming tendencies, fermenting glucose, lævulose, galactose, maltose, arabinose, dextrin, saccharose, lactose, salicin, and mannite, but not inulin,

¹ *Lancet*, February 15, 1908, p. 481.

dulcitate, or sorbite. It turns milk acid, but does not, as a rule, form a clot. It forms acid in bile salt lactose broth, precipitating the litmus and bile salts. When grown in broth, it forms considerable quantities of formic acid (Ainley Walker). If the broth be then filtered through a porous candle, the *S. rheumaticus* will fail to grow in the filtrate, while other forms of the streptococcus will grow well. Rosenthal considers this organism to be only a secondary or concomitant invader, and that the true infective agent is Achalmé's anaerobic bacillus, which he says is found in the blood, secretions, and tissues of rheumatic cases, both typical and atypical, but in these alone. Both *in vitro* and *in vivo* it can undergo transformation into a diplococcus. He has had a serum and a vaccine prepared of it, and advises the use of the serum only in severe cases, and of the combined serum and vaccine in the intervals between exacerbations. Whatever views may be taken of the true ætiology of these conditions, it yet remains that almost all the symptoms of acute rheumatism and its complications can be reproduced in animals by inoculation with living cultures of Poynton and Paine's organism, that, as we shall see, beneficial results can be provided in man by inoculation with a vaccine of it, and that the studies by Fordyce¹ and by Tunnicliffe² show that in acute rheumatism the opsonic index to this organism runs the definite course taken by that of all specific organisms in attacks of the disease which they produce.

Vaccine Treatment—Acute Manifestations.—The only adequate account of the treatment of acute rheumatism, endocarditis, and chorea by means of a vaccine of the

¹ 'International Clinics,' eighteenth series, vol. i., p. 40.

² *Journal of Infectious Diseases*, June 12, 1909, p. 346.

S. rheumaticus, is that given by Buchanan.¹ He employed a vaccine of the Wimpole Institute alone in fourteen cases, nine of these being acute pyrexial attacks with various complications, five of them being choreic with or without endocarditis. In five other cases, three of acute rheumatism and two of chorea, he employed salicylates as well. The initial dose was 5,000,000 or 10,000,000, being raised subsequently, if necessary, to 10,000,000 or 25,000,000. The main guidance as to dosages and intervals was afforded by the temperature chart and the clinical condition of the patient. Usually intervals were three to five days, occasionally a weekly one was used; rarely daily inoculations were found necessary. Buchanan concludes: 'The results have proved most encouraging. I have come to the conclusion that the vaccine has a definite effect upon acute rheumatism, and this is best seen when it is given early in the attack. In two cases it had definite results upon the endocarditis. In one it certainly prevented its onset where one would have expected it, for the attack was severe and accompanied by much arthritis. The arthritis rapidly disappears. There is no depressant effect. The fever subsides comfortably and easily. In more chronic cases it has a beneficial effect upon the joint lesions. In chorea it has a very beneficial effect, and in acute cases acts rapidly. It has a marked action in bringing down the pulse-rate. It may prove useful in the subsequent history of rheumatic cases to prevent relapse, but time will show this one way or another, and I would suggest that after an acute attack is over the vaccine should be administered at intervals for a considerable period to secure this effect. It acts best when given subcutaneously. I am of the

¹ *Journal of Vaccine Therapy*, vol. i., No. 1, p. 1.

opinion that we have in this method of treatment a sound and scientific addition to our armamentarium in combating rheumatic fever and chorea. I consider that this method of treatment deserves further trial, and that, acting, as I believe it does, upon the organism in the tissues, it will be found to have a preventive action on cardiac local lesions, and may be used over a long period as a prophylactic against recurrence, and to destroy the organism *in situ*.’

(For the full clinical histories of the cases with temperature and heart charts, and particulars of dosages and intervals, the reader should refer to the original article.)

CHRONIC RHEUMATISM.

It is by no means always easy to differentiate chronic arthritic conditions due to the *S. rheumaticus* from those which are grouped under the name of ‘rheumatoid arthritis,’ and may be due, as we have seen on p. 187, to other varieties of the streptococcus, as well as to other organisms. The clinical results obtained in a considerable series of cases reported by McLcod Veitch,¹ from the use of vaccines containing not only the *S. rheumaticus*, but other forms of the streptococcus, and other varieties of bacteria, would seem to indicate that there is often a combined invasion by several varieties of micro-organisms. The possibility of this will be readily admitted on reflection upon the great variety of clinical types presented in this disease-group, which may be called ‘chronic rheumatic and rheumatoid arthritis.’ Veitch makes no pretence of having worked out the causative organisms in any of his cases with scientific exactitude ; he only

¹ *Journal of Vaccine Therapy*, vol. i, No. 10, p. 269.

lays stress upon the elinical results obtained by treating these eases with a combined vaccine of *S. rheumaticus*, and of such other organisms as appeared to be eoncerned in the produetion of lesions elsewhere in the body, which might be regarded as primary or predisposing faetors to the chronic arthritism. He is eonfident that a suecessful result can best, and, indeed, in many eases, ean only, be brought about by the eontinuation of the *S. rheumaticus* vaccine with that of the other organisms. The eonsideration of the question as to what are to be regarded as predisposing faetors to the arthritism has already been fully dealt with (see p. 188). Veitch employed doses of 20,000,000 to 50,000,000 *S. rheumaticus* and streptoeoei of other types, 100,000,000 to 500,000,000 staphyloeoei and 100,000,000 to 500,000,000 of eoliform baeilli. The intervals at first with the smaller dose were from five to seven days ; later they were extended to a fortnight, or even a month. Treatment was often prolonged over six or twelve months or even longer.

In all he gives his results in twenty-seven eases. In some instanees they were so good as almost to amount to eures ; at least, the progress of the lesions appeared to be stopped, and the symptoms disappeared, not to reeur within a year or longer. In other instanees almost total failure to influence the eourse of the disease was eneountered. This, Veitch feels, was due to inability to deal adequately with the predisposing eauses. The results may be tabulated thus :

Total Number of Cases.	Greatly Improved.	Improved.	No Better.
27	13	8	7

His conclusions are that 'the great majority of, if not all, cases of arthritis owe their origin to the presence of a localized focus of infection somewhere in the body. In the treatment of arthritis we must therefore endeavour to find this focus of infection, and having found it, treatment should be directed with a view to its extermination. It is in this connection that vaccines have a useful field of application. I believe that the *M. rheumaticus* is intimately associated with arthritis. In acute and subacute rheumatism it may be the only infective agent. In cases of a rheumatoid nature, and in irregular varieties of arthritis, where there are distinct articular changes, the *M. rheumaticus* may also be implicated; but there is, as a rule, some other infective agent or agents at work.' A method of treatment which will bring about such improvement as is to be accounted almost entirely satisfactory in 50 per cent. of cases suffering from this distressing and refractory disease is obviously worthy of careful and extended trial.

MALTA FEVER.

The first attempt to influence the course of this disease by means of vaccine was made by Reid¹ in nine cases, who stated that a definite effect was produced thereby. Bassett-Smith² employed a vaccine made by heating agar cultures to 60° C. for half an hour in sixty-one cases of various kinds, from the severe undulant type to the intermittent. It was standardized by weight to contain 0.2 milligramme of dried organisms per c.c., the dose employed being from 0.25 to 0.5 c.c. Reference to the

¹ 'Annual Report of the Sanitary Commission with the Government of India,' 1905, p. 153.

² *Journal of the Royal Army Medical Corps*, 1908, p. 1.

table on p. 100 will show that the smaller of these doses corresponds to 700,000,000 organisms. The interval between injections was ten days. The negative phase induced by these doses was frequently very short or altogether absent, a steady rise being commonly observed. No relationship was found to exist between the curves of the opsonic indices and those of the agglutination reaction. Bassett-Smith concluded that the vaccine treatment appeared in a certain number of cases to produce a beneficial result, the severity of the symptoms being diminished, the general condition improved, and the duration of the disease curtailed ; but that in the more severe type of case with high fever and evidence of severe intoxication, a deleterious, rather than a favourable, effect was induced. The reason of this is not hard to find. So far as I can make out, Bassett-Smith was under the impression that the initial dose of 0.25 c.c. of the vaccine corresponded to about 50,000,000 organisms. In reality it corresponded to 700,000,000—a colossal dose with which to begin the treatment of a case of severe undulant fever, and even an excessive dose for cases with an intermittent temperature. Despite this overdosage, no definite ill effects were noticeable.

Wright¹ treated a chronic case under the guidance of the agglutination and opsonic index curves, which in this case ran a parallel course. After four inoculations (no particulars of dosage given) the temperature permanently assumed a normal level.

Kennedy² treated a chronic case with a bad prognosis with an autogenous vaccine. The temperature was re-

¹ 'Studies in Immunization,' p. 395.

² *Journal of the Royal Army Medical Corps*, September, 1910, p. 317.

mittent in type, rising to 102° to 103° F. The liver and spleen were enlarged, diarrhoea was present, and the patient much emaciated. On the 154th day of fever, a first dose of 100,000,000 was given. As this made the patient worse, only 7,500,000 were given eleven days later. Subsequent dosages and intervals were as follows: 6,000,000 after two days, 6,000,000 after four days, 9,000,000 after two days, 9,000,000 after two days. The evening temperature gradually and steadily fell to normal on the 184th day—*i.e.*, thirty days after the beginning of treatment—and did not again rise above it except on one or two isolated occasions, when a local abscess gave rise to some trouble.

Convalescence proceeded steadily, though somewhat slowly, as was only to be expected in a case of such prolonged and severe illness. The liver and spleen diminished in size, and the diarrhoea disappeared rapidly.

A few other cases are on record, and it would appear that if the treatment is to be of use in severe acute cases, a dosage of 5,000,000 to 10,000,000 and intervals of two to four days are advisable, while in chronic cases double this dosage at similar intervals may be safely employed.

PLAGUE.

The vaccine treatment of plague has so far been confined to preventive immunization as devised by Haffkine. For curative purposes, Yersin's serum has been largely used with, it is claimed, beneficial results, except in the pneumonic form.

The *B. pestis* produces a powerful endotoxin, a true exotoxin apparently being also produced, but in small amounts. Immunity appears to be due to the

production of bacteriolysin. According to Wright, the human blood possesses no bactericidal action, recovery being due to opsonic action and phagocytosis. Haffkine's plague prophylactic is prepared by growing the bacillus in flasks of broth to which a few drops of oil are added: to these latter the bacteria attach themselves, and form colonics, which hang down into the broth in the form of stalactites. By shaking the flasks from time to time these are detached, and others form in their places. After four to six weeks' incubation at 27° to 30° C., the cultures are sterilized by heating at 65° C. for one hour; their sterility is tested by cultures, and 0.5 per cent. carbolic acid then added. The dose of this vaccine is 3 c.c. for an adult man, 2.0 to 2.5 c.c. for a woman, and smaller doses for children, according to their age. It is stated that if a second inoculation is to be given in ten to fourteen days, the initial dosage may be reduced to 1 c.c. for men, 0.5 c.c. for women, 0.25 c.c. for children over ten, and 0.1 c.c. for children under ten. Local and constitutional symptoms of moderate severity ensue, and last for twenty-four to forty-eight hours, but do not, as a rule, necessitate the cessation of ordinary occupation. Immunity appears to be produced with rapidity, perhaps even within twenty-four hours, and lasts for twelve to eighteen months. Not only is the liability to infection much diminished, but also the case mortality. Thus, Haffkine¹ states that among natives the liability to infection is diminished to less than one-third of that occurring among the uninoculated, and that the case mortality is reduced by more than 50 per cent.; so that the total reduction of the death-rate among the inoculated is about 85 per cent. He also

¹ Proceedings of the Royal Society of Medicine, December 2 1907.

asserts—(1) that if in a European an attack subsequently occur, it always ends in recovery ; (2) that inoculation is applicable to persons already infected and incubating the plague, and that thereby symptoms are altogether prevented or much mitigated ; (3) that in natives the degree of immunity conferred appears to last through several outbreaks, whilst in Europeans it does not seem to have yet disappeared during the ten years since the inauguration of the method.

The general opinion in India is that absolute safety is insured for at least three months. As with antityphoid inoculation, a second administration of the vaccine in ten to fourteen days appears to confer an additional immunity.

Pfeiffer advises that the vaccine be prepared from two-day-old agar cultures, emulsified with broth or salt solution, and sterilized at 65° C. for one hour ; while Strong has suggested the use of living attenuated bacilli, and has employed such a vaccine at Manila without any ill results. He states that the mortality among those immunized in this way has been only 16·6 per cent., as compared with the 66·6 per cent. observed at the same time among the uninoculated.

In view of the likelihood that the first result of an inoculation with any of these vaccines is to produce an increased susceptibility, the simultaneous administration of 10 to 25 c.c. of Yersin's or of Lustig's antitoxie serum has been recommended.

SCARLET FEVER.

The view has steadily grown in favour of late that streptococci are intimately connected with the complications of scarlet fever, if not with the pathogenesis

of the fever itself. Thus, in over 70 per cent. of cases with albuminuria, streptococci are copiously voided in the urine, and in about 15 per cent. of cases without albuminuria. Bearing this in mind, Banks¹ has studied the variations in the opsonic index of the blood to streptococci as the disease progressed. He found that in cases running a fairly normal course the opsonic power towards streptococci varies in a pretty definite and constant way. It is decreased during the early febrile period, and rises to normal or above normal during the defervescence and general decline of symptoms. It falls during the second and third weeks, and even in uncomplicated cases the index may then be comparatively low. There is an increase to normal or over during the fourth and fifth weeks. In fatal cases with severe angina the opsonic power is markedly subnormal. Complications alter the usual curve, causing both absolute and relative differences. Thus, the opsonic power is decreased at the onset and during the earlier period of albuminuria and secondary adenitis; as convalescence is established the index rises. The opsonic values do not furnish many data for prognosis, but, in general, a persistent low index during nephritis or other serious complication is an unfavourable sign.

The author therefore thought it worth an effort to determine whether the course of scarlet fever could be favourably influenced by the administration of a vaccine prepared from the streptococci isolated from the throats of scarlet fever patients. From the throats of each of twelve such cases the *Streptococcus conglomeratus*, both of the small and large types, was recovered, and with great difficulty a mixed vaccine was prepared. The effect

¹ *Journal of Pathology and Bacteriology*, October, 1907, p. 113.

of this was then tested, in conjunction with Dr. Goodall, in six cases of uncomplicated scarlet fever, but apparently without producing the slightest good effect. Doses varying from 10,000,000 to 50,000,000 were employed.

Although this result was very discouraging, it has no bearing upon the value of the treatment by means of autogenous streptococcal vaccines of such complications as angina, adenitis, otitis, and nephritis. These are nearly always much benefited by the treatment. One case of scarlet fever with complications, in which the vaccine treatment almost certainly saved the patient's life, has been described by the author:¹ A boy, aged eleven, had eight weeks previously contracted scarlet fever. Apparent convalescence was followed by a fresh attack. At the end of a fortnight he was in a low muttering delirium, with a pulse of 128, somewhat irregular, but full and fairly strong, and a temperature of 104° F. Both drums had perforated, and were discharging freely. Cultures, both from the ear and blood, showed *Staphylococcus aureus* and *Streptococcus conglomeratus*. Within twenty-four hours a vaccine of the former was prepared, and an injection of 8,000,000 given, along with 12,000,000 of a stock vaccine prepared from twelve strains of *S. conglomeratus*. The temperature and pulse began to improve almost immediately, as will be seen from the table on p. 297. Consciousness was regained within twenty-four hours, sleep was good, and the following morning he was wanting to know what he could have to eat. The preceding injection was then repeated, and again three days later, the temperature oscillating daily between 99° and 101° F. Convalescence was uninterrupted, and fifteen days after the first injection the patient was up in a chair for two

¹ *Lancet*, September 11, 1909, p. 780.

hours. The aural discharge rapidly lessened, but, to minimize the damage as much as possible, a few injections of 100,000,000 staphylococci and 25,000,000 streptococci were given on the eleventh day of treatment, and at subsequent intervals of ten days. Ten weeks afterwards hearing was quite normal on both sides.

Date and Time of Injection.			Pulse.	Rectal Temperature.
				°F.
April 19,	8. 30 p.m.		128	104·8
April 20,	3 a.m.		116	103·8
	7 a.m.		120	103·6
	11 a.m.		110	103·2
	3 p.m.		108	103·0
	7 p.m.		104	101·8
	11 p.m.		110	102·8
April 21,	3 a.m.		104	102·4
	7 a.m.		116	100·0
	11 a.m.		96	100·4

Boughton and Weaver,¹ have also tried to influence the course of scarlet fever in eighty-eight cases by the use of a streptococcal vaccine sterilized by the addition of 25 per cent. galactose. Although it was administered as early in the attack as possible, they could not detect that it had any influence for good either on the ordinary course of the disease or on the incidence of complications. On the other hand, they employed it in the treatment of thirty-one cases of streptococcal complications when these had arisen and tended to become chronic, and found that in a considerable percentage of the cases prompt improvement followed.

On the other hand, Gabritschewsky and others have performed a very large number (37,000 up to April, 1908)

¹ *Journal of Infectious Diseases*, 1908, p. 608.

of prophylactic inoculations in Russia with a vaccine of a streptococcus isolated from a case of scarlet fever, and sterilized by heat at 60° C. The statistics they supply would seem to offer convincing evidence of the utility of the procedure. In two villages where scarlet fever broke out, all the children were immediately inoculated. In the one village no more cases occurred among the children, but two uninoculated adults contracted the disease. In the second village all escaped but one uninoculated child, who came thither on a visit, and one child in a family of seven. This one had hidden herself to escape inoculation, and contracted the disease in four days. The other six were not attacked. In certain other villages in which the incidence among the uninoculated varied from 15 to 70 per cent., 4,771 received inoculations. Of these 2,034 had two or three injections. Only two of these were attacked; 2,737 had only one injection, and of these 41 were attacked, but most only very mildly. Immunity is supposed to last for one and a half years.

Jochmann and Michaelis,¹ while not regarding the streptococcus as the specific cause of the disease, yet consider it the cause of many dangerous complications. They therefore compared the results obtained by using an antistreptococcic serum alone, a vaccine alone, and the combined serum and vaccine. They consider that the last form of treatment gave the best results. They employed the various methods to 52 severe cases which occurred in a total of 400 cases. Of these 14 died and 38 recovered without complications of any kind. The total absence of nephritis they regard as more than a mere coincidence. Within their previous experience it

¹ *Berliner Klin. Woch.*, May 16, 1910.

was very rare for any patient to recover from whose blood streptococci could be isolated, whereas among those who recovered under the combined treatment, there were a number who belonged to this category.

Contrary to my very limited, and Boughton and Weaver's more extended, experience, it would thus appear that a vaccine of *Streptococcus conglomeratus* is of decided service as a prophylactic agent, and of a distinct but more limited service as a curative agent in the course of the disease.

HYDROPHOBIA, OR RABIES.

Although the infective agent in this disease has not yet been observed or isolated, there is no doubt of its existence, or of the fact that the results achieved by the preventive inoculations of Pasteur depend for their success on its presence in the vaccine. It has therefore been deemed advisable to make mention of antirabic inoculation, if only to draw attention to the recent work of Semple,¹ whereby he has discovered a method of preparing a safe and efficient vaccine which will keep, and is easily obtainable, thereby doing away with the elaborate methods of Pasteur and the necessity of attendance at a Pasteur institute. Fermi and others have employed somewhat similar methods. Semple takes the medullas of rabbits which have died after inoculation with rabies, makes thereof an 8 per cent. dilution in normal salt solution, to which 1 per cent. carbolic acid has been added. This dilution is then kept for twenty-four hours at 37° C., diluted with an equal volume of sterile normal salt solution, and stored in a cool place away from the light. Semple has shown that this 4 per cent. dilution in 0.5 per cent.

¹ 'Scientific Memoirs of the Government of India,' No. 44.

carbolic acid normal salt solution is a safe and efficient vaccine for the immunization of susceptible animals like the monkey, dog, and rabbit, against subdural inoculations with virulent living virus. The serum of inoculated animals gives a well-marked rabieidal action on living virulent virus, and it would seem that this should also prove to be a safe and efficient antirabic vaccine for the prophylactic treatment of persons bitten by rabid animals.

SLEEPING SICKNESS.

Although no attempt has yet been made to treat this disease in man by means of a vaccine, the experimental work on animals by Schilling¹ has led to such results as may justify the expression of the hope that this means of treatment will be tried ere long. Schilling took rats, heavily infected with the trypanosome of nagana, and bled them into broth containing 2 per cent. sodium citrate. The mixture was then centrifugalized, the upper turbid layer drawn off with a pipette, and mixed with an equal amount of broth containing tartar emetic 1 part in 700. The fluid was again centrifugalized, the sediment mixed with a small quantity of broth, and allowed to stand for at least two hours. One-half to 2 c.c. of the resultant vaccine injected into the peritoneal cavity of a rat produced in twenty-four hours a distinct immunity against trypanosome infection.

¹ *Deutsch. Med. Woch.*, No. 1, 1912.

CHAPTER X

DISEASES OF THE EYE

Disease of the	Infective Agents.
Lids	Staphylococcus, streptococcus.
Conjunctiva	Gonococcus, pneumococcus, bacillus of Friedländer, streptococcus, staphylococcus, <i>B. coli</i> , <i>B. pyocyaneus</i> , <i>M. ps-catarrhalis</i> , Koch-Weeks bacillus, Morax-Axenfeld bacillus, <i>B. tuberculosis</i> .
Lachrymal sac ..	Streptococcus, pneumococcus, staphylococcus.
Cornea and sclera ..	Gonococcus, pneumococcus, streptococcus, staphylococcus, <i>B. coli</i> , <i>B. pyocyaneus</i> , <i>B. tuberculosis</i> .
Iris and ciliary body ; retina and choroid	{ Gonococcus, pneumococcus, streptococcus, staphylococcus, <i>B. tuberculosis</i> .

PRELIMINARY CONSIDERATIONS.

Several considerations strongly favour an extended application of vaccine therapy to diseases of the eye. Among these may be mentioned—(1) the small likelihood of any further marked advances in surgical treatment pure and simple ; (2) the extreme rapidity with which certain infections progress, and the gravity of the resultant tissue destruction ; (3) the liability to sympathetic involvement of the other eye ; (4) the excellence of the guidance as to appropriate dosage, and intervals afforded by clinical observation of the diseased parts ; (5) the

facility with which the antibodies can be brought to the foci of infection by the excellent blood-supply to the parts, the cornea and sclera alone excepted.

The success which should attend on therapeutic inoculation is fully realized in actual practice. Personally, in an experience covering nearly every known bacterial infection of the eye, I have only encountered two or three partial failures, and these have been in slowly progressive corneal ulcerations, in which all the resources of surgery had been already exhausted, and in which there were these two obstacles to success—a very limited lymph-supply to the parts, and a grave doubt as to the precise nature of the bacterial infection. As the great majority of my cases either had proved extremely refractory to other methods of treatment, or were of such great severity that the prognosis was very bad indeed, I cannot help feeling that vaccine treatment is an indispensable adjunct to other methods, and that it has been so unduly neglected by ophthalmic surgeons in general, that the pioneer work I carried out during the years I was pathologist at the Royal Eye Hospital has been almost wasted.

If the desired measure of success is to be achieved, several things must be carefully borne in mind, such as—

1. That some infections—viz., pneumococcal and gonococcal hypopyon ulcers—progress with such rapidity that treatment should be begun at the earliest possible moment. As soon as a tentative diagnosis has been made from stained films of the secretion, a full dose of a stock polyvalent vaccine should at once be given, and the preparation of an autogenous vaccine rapidly proceeded with.

2. That ocular disorders may be only secondary manifestations of a primary infection elsewhere. While recent observations have shown, on the one hand, that the

Treponema pallidum is itself resident in the tissues of an interstitial keratitis, on the other hand, they have shown that phlyctenules may be induced by the toxins alone of the tubercle bacilli, the bacilli themselves being not essential for their production ; and that irido-cyclitis and choroiditis may be the result of toxic absorption from the gums or bowels. It therefore follows that careful search for primary foci of disease elsewhere in the body must often be made in order to arrive at the correct determination of the nature of the infection.

3. That inasmuch as a correct bacterial diagnosis is essential to success, care must be taken to employ media which will favour the multiplication of eye organisms. As these are often highly hæmophylic, it is necessary always to employ tubes of blood-agar, blood-serum, and serum-agar for cultural purposes. Care must also be taken to exclude extraneous organisms. This is best done by washing the eye out thoroughly with sterile water, applying a sterile pad for half an hour to the eye in such a way that opening and closing of the lids is not prevented, and then taking specimens both from the upper conjunctival sac and at the caruncle. In cases of corneal ulcerations, scrapings should be taken from the advancing edge after the above preliminaries have been carried out.

4. That in all diseases of the cornea and sclera full doses of vaccine are essential if a good result is to be insured. The blood-supply to these parts is so poor that the quantity of circulating antibodies must be greatly raised if an adequate quantity is to reach the infected parts. Good results have, I know, been reported from the use of small dosages, but so have many failures. On the other hand, I have never seen either a failure or any harm

result from the use of large doses. The "negative phase" is here, more than anywhere else, an utter bogey. In all cases of ocular disease where the prognosis is very bad it is much the best procedure to act boldly, and give such a dose of vaccine as will be sure to excite the formation of adequate immune bodies if the tissues are capable of making a response.

DISEASES OF THE LIDS.

Bacteriology.—Whether the disease be a blepharitis, chalazion, or hordeolum, it is usually due to a staphylococcus, rarely to a streptococcus.

Preliminary Considerations.—Errors of refraction should always be corrected and ordinary forms of treatment first be tried. If recurrence proves troublesome vaccine treatment should be resorted to.

Vaccine Treatment.—Initial doses of 100,000,000 to 250,000,000 staphylococci and 25,000,000 to 50,000,000 streptococci may be repeated or increased at weekly intervals. Treatment should be continued till complete cure appears to have resulted, and a series of three progressive doses should be given about every six months to prevent recurrence. The results should be uniformly successful.

For an account of a series of cases, see Mayou (*Ophthalmoscope*, 1908).

DISEASES OF THE CONJUNCTIVA.

Bacteriology.—A great variety of bacteria are capable of setting up inflammation of the conjunctiva. The acute forms may be due to the Koch-Weeks bacillus, gonococcus,

pneumococcus, streptococcus, staphylococcus, bacillus of Friedländer, *B. coli*, *B. pyocyaneus*—while Rossiter has described an interesting form very common in Samoa, and leading to corneal opacities due to a Gram-negative coccus of the *M. catarrhalis* group;—the chronic forms to the diplobacillus of Morax-Axenfeld, the bacillus of Friedländer, the staphylococcus, and the *B. tuberculosis*.

In young children the gonococcus, staphylococcus, and Koch-Weeks bacillus are most commonly found; in old people the bacillus of Morax-Axenfeld and the staphylococcus. For conjunctivitis due to trauma, the pneumococcus, streptococcus, and *B. pyocyaneus* are usually responsible.

Preliminary Considerations.—In the commonest form of the disease—viz., the acute variety due to the Koch-Weeks bacillus—the ordinary methods of treatment almost invariably suffice to bring about rapid cure. Some of the other forms—viz., those due to the bacillus of Friedländer and *B. tuberculosis*—are exceedingly resistant to ordinary measures. Between these extremes are those which usually do well but sometimes do very badly. In the latter event the result to the patient may be very serious indeed. This is especially likely to be the case with regard to the gonococcal and pneumococcal forms, and in all cases which are the result of trauma. I would therefore strongly advocate the routine use of vaccines in these cases, for thereby an invariably successful issue should result provided treatment is commenced sufficiently early in the attack and adequate doses are employed. Reliance will not, of course, be placed on the vaccine alone, but all such other measures, both curative and preventative of extension, as experience indicates, should simultaneously be employed.

Vaccine Treatment.—The particular advantages which are to be anticipated from vaccine treatment are increased rapidity of cure, and limitation of extension to and of damage of adjacent parts, so that unimpaired vision may be left ; but, as I have already said, these good results can only be insured by the use of full dosages. Good results may be obtained at times by small dosages, but many failures are sure to be met with. Thus Bryan¹ mentions two cases—one in a man, both of whose eyes were infected by the gonococcus, resulted in cure, with normal vision, in one month with dosages of 1,000,000 to 2,000,000 given at intervals of six to ten days ; the other, in a boy of twelve, with gonococcal conjunctivitis of one eye, resulted in perforation, prolapse of the iris, and loss of vision. Similar dosages and intervals were employed. Now, I do not wish to be unduly critical of another man's methods, but I do claim to have such experience of this condition as to be justified in stating confidently that possibly one dose, and certainly two doses, of 250,000,000 would have cured both these cases completely in seven to ten days.

The initial dosages for adults which I have found to be devoid of danger, and yet sufficient to produce an almost invariably good result in acute cases, are as follows : Streptococcus, *B. coli*, *B. pyocyaneus*, 100,000,000 ; pneumococcus, gonococcus, 250,000,000 ; staphylococcus and bacillus of Friedländer, 500,000,000. These may be repeated at intervals of three days, and increased dosages at intervals of five days. Smaller dosages than these should *never* be employed if perforation threaten. The following case illustrates well the effect which may be produced by adequate dosages : When I was in charge of the vaccine department at the Royal Eye Hospital, an

¹ *British Medical Journal*, March 23, 1912, p. 663.

out-patient came to see Professor McHardy with a gonococcal conjunctivitis of one eye of such severity that three members of the staff to whom I showed the case in Professor McHardy's absence agreed in giving a hopeless prognosis. There was a complete hypopyon, but no apparent ulceration, of the cornea. I therefore assumed the responsibility of at once giving an inoculation of 250,000,000. Although the patient was extremely negligent of himself, and could not be induced to use a lotion or guard to the other eye, improvement began within twenty-four hours. On the fourth day there was little chemosis or discharge, and on the eighth day cure was practically complete. Indeed, when the patient was shown to Professor McHardy, the latter, after a preliminary examination, inquired the reason of the man's attendance.

The details of three other cases with complications will be found under diseases of the cornea, and so consistently successful have my results been that I feel fully justified in assuming the attitude I do in regard to the question of dosage.

In metastatic inflammation of the conjunctiva smaller dosages seem to give as good results, and half the above doses may be employed unless a further reduction is indicated by the nature of the primary focus.

In infants and young children, a dosage about one-fifth of that used for an adult will be found appropriate.

One special form of acute—or, rather, subacute—conjunctivitis may be mentioned. I refer to that form which appears in infants about fourteen days after birth. This I have found to be due to a staphylococcus, probably derived from the mother's vagina. The instillation of silver nitrate at birth does not seem to prevent its onset, and at times it proves exceedingly refractory to treat-

ment. I have secured excellent results, however, by giving 100,000,000 of the autogenous vaccine by the mouth the first thing in the morning. Hypodermically, 25,000,000 to 50,000,000 may be administered.

Rossiter has tried the administration into the conjunctival sac daily of 25,000,000 of a vaccine of the causative organism in the Samoan conjunctivitis referred to on p. 305. He concluded that instillations of 5 per cent. protargol give better results, but great exception must be taken to the method of administration of the vaccine.

CHRONIC CONJUNCTIVITIS.—At times ordinary methods of treatment prove of no avail, even in cases due to the diplobacillus of Morax-Axenfeld. A vaccine, on the other hand, I have never found to fail ; but if a blepharitis coexist, this must simultaneously receive appropriate treatment. Parinaud's variety, which is probably due to a staphylococcus, seems to give the least satisfactory result.

In the diplobacillary form, treatment should be begun with a dose of 100,000,000. If improvement be not already manifest in seven days, one of 250,000,000 should then be given, and may be repeated in another seven days. Only rarely will further treatment or increased dosages prove necessary.

Bryan¹ treated one case of ten years' standing with doses of between 10,000,000 and 50,000,000. That five months' treatment was necessary to bring about an almost complete cure is again to be attributed to too small dosage.

The form due to the bacillus of Friedländer is exceedingly refractory to ordinary measures, but will usually

¹ *Loc. cit.*, p. 664.

yield rapidly to adequate doses of vaccine—dosages and intervals as for the bacillus of Morax-Axenfeld.

Conjunctivitis due to *B. tuberculosis* assumes various clinical forms, and upon the clinical characteristics depend partly the results to be anticipated from ordinary surgical treatment, and also the necessary duration of a course of vaccine treatment. In the nodular form especially, treatment may have to be very prolonged, but patience will secure a cure in the great majority of instances. Tuberculous conjunctivitis is, as a rule, secondary to infection elsewhere, and the variety of the organism at work requires some consideration in order to guide in the choice of the suitable tuberculin.

Old tuberculin, I think, is definitely contra-indicated in all forms of ocular tuberculosis, and the bacillary emulsion is preferable to the T.R. In order to remove all doubt as to whether the appropriate strain of tuberculin is being employed, the best procedure is to employ a mixture of the human and bovine types. I am convinced that the mixture of human and bovine bacillary emulsion will give more uniformly good results than will the human type of T.R. This applies to all forms of ocular tuberculosis. Relatively small dosages seem to give good results, but if the case appears to be hanging fire, the initial dosage of 0.00001 c.c. mixed B.E.'s may be steadily increased at seven-day intervals until progress is evidenced. Subsequent increases should then be made much more gradually. Bryan¹ and Ormond and Eyre² each record one very good result. Von Hippel³ complete success in three cases treated by initial doses of

¹ *British Medical Journal*, March 16, 1912, p. 590.

² *Transactions of the Ophthalmic Society*, vol. xxviii

³ *Arch. f. Ophthal.*, Bd. vi., 59, p. 1.

0.0002 c.c. T.R., which were increased by 0.0002 c.c. at each administration, these being given every alternate day until a dosage of 0.002 c.c. was attained. The increments were then by 0.002 c.c., until 0.02 c.c. was given; then by 0.02 c.c. until 0.1 c.c. was given. If the temperature rose above 100° F. at any time, the previous dose or a smaller one was given until no temperature reaction occurred. Torok¹ also records five successful cases.

Good results may therefore be anticipated if treatment be conducted under the guidance of clinical symptoms, and be continued for a period of six to twelve months.

DISEASES OF THE LACHRYMAL SAC.

These usually yield to ordinary measures, but trial should always be made of vaccine treatment before resort is made to extirpation. Chronic dacryocystitis, as Eyre has shown, is almost invariably a sequela of an acute conjunctivitis, but, as a rule, the organisms of the latter affection become supplanted, usually by the streptococcus, occasionally by the pneumococcus or staphylococcus.

In a few cases where surgical measures appeared to be failing, I have obtained cures by the administration of 100,000,000 initial doses of the autogenous vaccine. These were increased gradually, in some instances at intervals of seven to ten days, until an ultimate dosage of 500,000,000 has been attained. Cure has usually resulted in six to eight weeks.

DISEASES OF THE CORNEA AND SCLERA.

Bacteriology.—For the ulcerative forms, a great variety of bacteria may be responsible, as with those of acute

¹ *Archives of Ophthalmoscopy*. September, 1907.

conjunctivitis. Interstitial keratitis, phlyctenular keratitis, and episcleritis are, as a rule, tuberculous in origin (excluding, of course, the *Treponema pallidum* as a causative organism), but secondary infection by other organisms, such as the staphylococcus, may be super-added.

Vaccine Treatment.—The vaccine treatment of acute ulcerative conditions of the cornea is precisely similar to that of cases of acute conjunctivitis. The prime thing to bear in mind is the necessity of adequate dosage. Some of the forms, such as those due to the gonococcus, pneumococcus, and streptococcus, advance with such rapidity that, unless progress is checked almost immediately, perforation is almost certain to ensue. What vaccine treatment can accomplish is well shown by the description of the following three cases in which I was responsible for the inoculations. Two of these cases were under the care of Dr. Willoughby Lyle, who has very kindly furnished the following notes :

‘ A male, aged forty-nine, was suffering from a rapidly infiltrating corneal ulcer, with hypopyon two-thirds up the aqueous chamber. Local treatment was persevered with for twelve days without any improvement whatever taking place ; in fact, the intra-ocular tension was raised and the local pain so great (and there was no perception of light) that it was almost decided to excise the eyeball. Vaccine therapy, however, was commenced, and local treatment persevered with. In four days the hypopyon began to disappear, and the cornea to clear at the margins. From that time until the patient left the hospital—four weeks later—the eye gradually improved. Altogether two injections of 250,000,000, and one of 500,000,000, pneumococci were given. On examination two days

after leaving the hospital, the local condition was as follows : There was a large irregular leukomatous patch, somewhat vascular, over the lower two-thirds of the cornea, a narrow ring of clearer cornea below the leukoma. The margin of the pupil could just be seen over the nebulous cornea above. The intra-ocular tension was normal, and the patient could distinguish between light and darkness.

‘ The second case was in a child, aged three years seven months, who was admitted into the hospital with a central corneal ulcer with infiltrating margins and a small hypopyon. In spite of local treatment, the hypopyon increased, the ulcer spread, and the cornea ruptured. Vaccine treatment was commenced with a dose of 175,000,000 pneumococci, and from that time the eye began to clear. When the child left the hospital there was a large “ leukoma adherens ”; the cornea was somewhat vascular ; there was a well-formed aqueous chamber ; the iris was a good colour, and reacted readily to light.

‘ The favourable result obtained in these cases was very largely due to the vaccine treatment, and but for it the first-mentioned patient would undoubtedly have lost his eye.’

The third case was under the care of Mr. L. V. Cargill, and was a very severe one. As soon as the pneumococcus was isolated, a dose of 250,000,000 of the pneumococcal vaccine which had been prepared for Case 1 of Dr. Lyle’s was given. Improvement began within twenty-four hours, and progressed with extreme rapidity. The hypopyon was rapidly absorbed, and the patient discharged within a week.

Results precisely similar to these I have also obtained in cases due to the gonococcus and streptococcus.

Numerous other successful cases have been recorded by other observers. Thus, Grey Edwards¹ reports three cases of hypopyon ulcer treated with staphylococcus vaccine. The first, an acute case, rapidly recovered after one dose of 250,000,000 ; the second after one injection of 100,000,000 ; and the third after three inoculations. Subconjunctival injections of mercuric cyanide were also given.

Bryan² cured one case of hypopyon ulcer in a man aged sixty-four with a pneumococcal vaccine. A small hypopyon disappeared within twenty-four hours of the administration of a dose of 15,000,000 of a stock vaccine. Eight days later 30,000,000 was given, and next day the ulcer healed. Five days later, although the eye was quiet, 50,000,000 was given. In another severe case, in a man aged seventy-seven, one dose of 25,000,000 failed to stay the acute ulcerative process. De Schweinitz³ has also recorded the successful treatment of a streptococcal hypopyon ulcer with three doses of 50,000,000, 100,000,000, and 100,000,000. A few unsuccessful cases are also on record, but in these, without exception, absurdly low dosages were employed. As said before, upon the question of dosage would seem entirely to depend the issue of the case, provided the clinical condition is not beyond all hope.

Three interesting cases of chronic corneal ulceration—two due to the pneumococcus, and known as ‘*ulcus serpens corneæ*,’ the third due apparently to an organism of the *M. catarrhalis* resembling that described by Rositer (see p. 305) as the cause of Samoan conjunctivitis—were treated by me at the Royal Eye Hospital. In the

¹ *Ophthalmoscope*, 1908, p. 79.

² *Loc. cit.*

³ *Therapeutic Gazette*, October 15, 1910.

two pneumococcal cases a completely satisfactory result was secured. The details of one of them are as follows : The patient was a man, eighty years of age, under the care of Mr. Brookbanks James, and was admitted with a very bad corneal ulcer. A large hypopyon was present ; the cornea was very opaque, the iris bound down by adhesions, and the tension $+1.5$. Cauterization, paracentesis, and, later, sclerotomy for the relief of tension and evacuation of the hypopyon, brought only temporary improvement, and excision seemed the only remedy. The condition was still acute when the pneumococcus was isolated and a vaccine prepared. Despite the high index to this organism—viz., 2.5—an injection of 250,000,000 organisms was given. Within three days the eye began to improve in appearance ; at the end of a week the index was 4.2, and after a fortnight 3.0. A second injection was then given, with the result that, eighteen days later, the index stood at 6.3, and the inflammation had quite subsided. A large partial staphyloma of the cornea which developed later was treated radically by excision without the use of sutures. No reaction followed the operation, and the final result was an eye in which some slight vision was preserved, and a firm flat scar in the cornea left in the site of the staphyloma. Several months later the eye was quite quiet and free from irritability.

The third case was under the care of Professor McHardy. The patient had already had one eye removed for chronic ulcerative keratitis, going on to perforation, shrinking of the globe, and considerable pain. About eighteen months subsequently the second eye was also attacked : general superficial erosion of the cornea went on to infiltration of the more superficial, then of the deeper

layers of the cornea ; the tension fell considerably and vision was practically nil, only dim perception of light being possible. Cultures from the surface of the globe yielded large cocci not staining by Gram's method, which were apparently not the *M. catarrhalis*, and diplococci which morphologically resembled the pneumococcus, but could not be isolated. Upon the chance of the infection being a pneumococcal one, two injections of a vaccine were given without producing any good result ; on the contrary, the condition became rather worse. The vision was so bad that an iridectomy was decided on. The iris, when seized by the forceps, simply tore at once, it was so pulpy ; cultures were made from this small portion of iris and from scrapings of an eroded portion of the cornea, and the same non-Gram-staining coccus obtained from both. The organism was not identified, but a vaccine was made of it as a last hope. A first injection of 250,000,000 organisms, the index being 0·5, was followed, ten days later, when the index was 0·8, by a second of like amount ; seventeen days after the first injection, the index being 1·5, the eye began definitely to improve, and steadily continued to do so. Twenty-eight days after the second injection the index was 2·6, and a further dose of 400,000,000 given. The eye was now very much better ; vision was returning, fingers being seen at about 1 foot. In another twenty-six days the patient could discern faces fairly well, and a further injection of 500,000,000 cocci was given. A fortnight later vision was further improved, and the patient was discharged. When seen two months later, vision, both near and for distance, = $\frac{1}{80}$: the cornea was diffusely nebulous ; the eye was quite quiet, and vision had decidedly improved since the patient had left the hospital.

In interstitial keratitis, phlyctenular keratitis, and episcleritis, when tuberculous in origin, good results are, as a rule, obtained. What has been already said as regards choice of tuberculin, dosage, and intervals under 'Tuberculous Conjunctivitis' holds with equal force for these affections. Due consideration must be paid to any other foci of tuberculous disease, and to the local presence of any concomitant invaders, such as the staphylococcus. Treatment, especially in the case of keratitis, may have to be very prolonged.

Jones¹ gives the results obtained at St. Mary's Hospital in nine cases of tuberculous phlyctenular keratitis, three of which had mixed infection, as follows: Five were much improved, three improved, and one, in which a large variety of contaminating organisms was present, was unchanged. This is a very fair statement of the results to be expected from a course of treatment of only three to six months' duration, as was conducted in these cases.

Bryan² treated twenty-two cases, including one of interstitial keratitis, with satisfactory results in every instance except that of a boy with enlarged cervical glands. A larger dosage than his maximum of 0.00002 c.c. of B.E. might also here have yielded a better result.

Derby³ has treated nine cases of interstitial keratitis with good results.

The uniform success achieved in these conditions would seem to place the efficacy of tuberculin beyond all question.

¹ *Loc. cit.*, p. 141.

² *Loc. cit.*, p. 591.

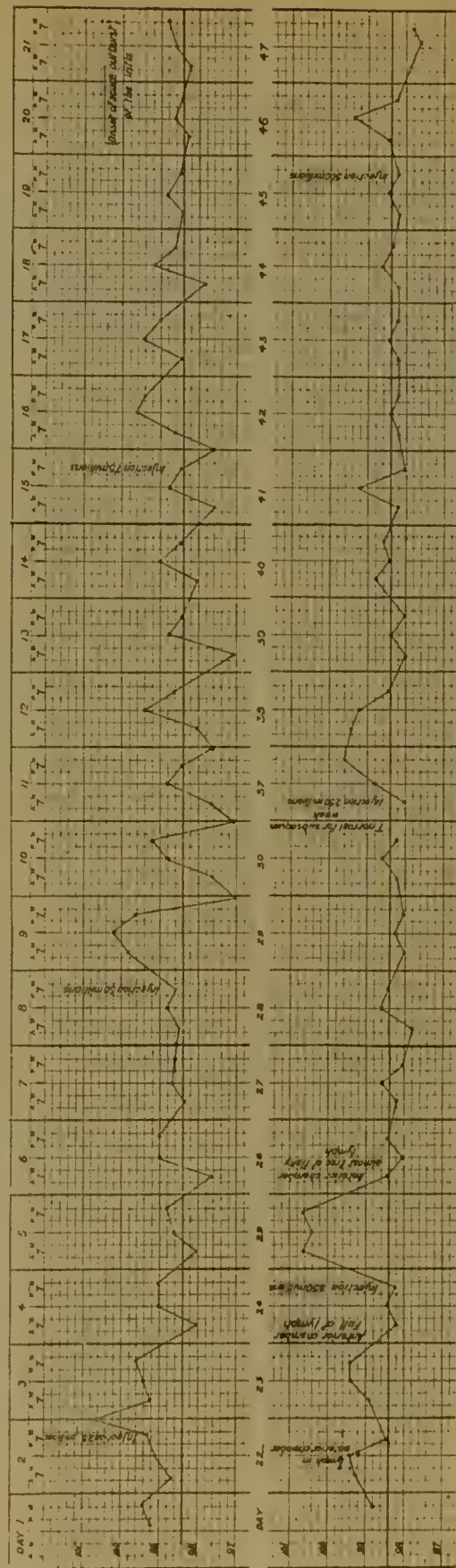
³ Transactions of the American Ophthalmic Society, 1910, vol. xii., part ii., p. 614.

DISEASES OF THE IRIS AND CILIARY BODY, RETINA AND CHOROID.

The tuberculous varieties should yield such consistently good results if treated on the lines already laid down that nothing further need be said. There are, however, two or three varieties of especial interest, such as gonococcal and pneumococcal irido-cyclitis, rheumatic iritis, and toxic choroiditis. The first two forms are mentioned merely to enable me again to impress the importance of adequate dosage, which I think is best done by recording the following case :

The patient was a male aged thirty-three. He had had three attacks of acute gonorrhœa, fourteen, eight, and two years prior to the present trouble. The last attack was complicated by gonorrhœal rheumatism in the knees, back, shoulder, and other joints, and from this little relief had been obtained by the various measures employed, which included a course of baths at Harrogate. In February, 1909, there was an attack of syphilis, for which a full course of rubbings was performed at Aachen, at the end of which the Wassermann test gave a negative reaction on two occasions. Prior to coming under my care he had had several slight attacks of iritis and more or less continuous rheumatism, for which he had been taking aspirin regularly, without much result other than that of completely upsetting the digestive system. When I saw him early in October, 1909, the following symptoms presented themselves : Chronic urethritis with considerably enlarged prostate and seminal vesicles ; subacute iritis in the right eye, with old adhesions in the left eye ; multiple arthritis, especially bad in the case of lumbar and cervical spine, one knee, and both ankles. A few days' rest at home,

CHART X.—TO ILLUSTRATE THE CONDUCT OF A COURSE OF THERAPEUTIC INOCULATIONS UNDER GUIDANCE OF THE TEMPERATURE
IN A CASE OF COMPLICATED GONOCOCCAL INFECTION. (For description see p. 317 *et seq.*)



where mild irrigation of the urethra was performed, and the pupils dilated, culminated in an exacerbation of the iritis and acute prostatitis, whereupon the patient was removed to a nursing home. Here complete rest was secured, and local and constitutional treatment directed against the iritis, arthritis, and urethritis. In addition, a course of vaccine treatment was decided on ; but a formidable difficulty arose in connection with the dosage to be employed. Previous experience indicated an initial dose of 10,000,000 to 25,000,000 for the prostatitis, 50,000,000 to 75,000,000 for the urethritis, 250,000,000 for the iritis, and 500,000,000 for the arthritis.

As the arthritis was no worse than it had been, the iritis not very acute, but the prostatic pain severe, an initial dose of 25,000,000 was employed. The effect upon the temperature is to be seen in the chart (*vide* days 2 and 3). As the combined method of attack had produced a decidedly beneficial effect upon the prostatic and urethral condition, and the temperature was steady on the seventh day, a dose of 50,000,000 was injected upon the eighth day. This produced a marked effect upon the temperature, which continued to oscillate for six days. Upon the following day a dose of 75,000,000 was employed, with less disturbance of the temperature than on the preceding occasion, and upon the fourth day it was practically normal. Progress then seemed satisfactory ; the urethritis and prostatitis were certainly better, the joints rather less swollen and painful, the iritis quieter. Suddenly, upon the following day, there was marked exacerbation of the iritis. For this Mr. G. Brookbanks James prescribed active leeching, hot-packs, diaphoretic drinks, strong solution of atropine locally, and mercury internally. Despite these measures, the anterior chamber

three days later was full of flaky lymph, and the pain almost uncontrollable by injections of half-grain doses of morphia. The condition was rendered additionally serious by the fact that we could not be sure how much damage had been done to the other eye by previous subacute attacks. I therefore thought it well to remember my own dictum, that in gonococcal infection of the eye a dosage of 250,000,000 is the minimum of utility. This was accordingly administered, with some misgivings and no little fear of a resultant prostatic abscess. A marked reaction of the temperature followed, but after thirty-six hours the latter was normal and the anterior chamber nearly free from lymph. To what precisely this dramatic effect was due, it is of course impossible to say. The iritis was a very bad one, Mr. James declaring that he had only seen one or two worse. It had developed despite active local treatment, and disappeared within two days of the injection. For this, both Mr. James and myself could not help feeling that the vaccine treatment was largely responsible. The temperature remained practically normal, and no recrudescence occurred during the succeeding two years.

The latter two varieties—viz., what I have called ‘rheumatic iritis’ and ‘toxic choroiditis’—have proved alike a source of difficulty to the pathologist and the ophthalmic surgeon. Recent investigations into obscure arthritic diseases have established a much more definite connection between them and other foci of disease, whether located in the gums, intestines, urethra, or uterus, and just as we know that gonococcal irido-cyclitis may be set up metastatically during an acute gonorrhœal urethritis, so it appears that it may result many years after the infection has apparently disappeared. A further propor-

tion of the cases of irido-cyclitis of doubtful origin may be due to the gonococcus, but most are probably due either to the *Streptococcus rheumaticus*, to the streptococci of the mouth concerned in a coexistent condition of pyorrhœa alveolaris or follicular tonsillitis, or to a streptococcus or *B. coli* concerned in some intestinal or uterine disorder. The ophthalmic surgeon has been quite awake to these possibilities, but has failed to grapple with them adequately; and just as we have seen that vaccine treatment may greatly benefit an arthritis, so it is more than possible that it may prove of service in the iritic condition. Some support is lent to this view by the results obtained in a few cases. Thus Carmalt Jones¹ relates that a case of iritis associated with osteo-myelitis was very much improved and nearly cured in three months by the use of doses of staphylococcal vaccine carrying from 50,000,000 to 100,000,000, and that another case of choroiditis associated with pyorrhœa alveolaris improved considerably under doses of 30,000,000 of a mouth streptococcus. Careful investigation on these lines will almost assuredly prove productive of much useful information as to the true ætiology and best means of treatment of these intractable conditions.

¹ *Loc. cit.*, p. 141.

CHAPTER XI

DISEASES OF THE EAR, NOSE, AND THROAT

Disease of the—	Infective Agents.
External auditory meatus	Staphylococcus, streptococcus, <i>B. coli</i> , diphtheroid bacilli.
Internal ear and mastoid cells	Staphylococcus, pneumococcus, streptococcus, <i>B. influenzæ</i> , <i>M. catarrhalis</i> , bacillus of Friedländer, <i>B. coli</i> , <i>B. proteus</i> , <i>B. pyocyaneus</i> , <i>B. diphtheriæ</i> , and diphtheroid bacilli, <i>B. typhosus</i> , <i>B. tuberculosis</i> .
Nose, antrum, and various sinuses	As for the internal ear, with addition of <i>M. paratetragenus</i> , bacillus of Frisch, bacillus of Abel, <i>B. lepræ</i> , and <i>Streptothrix actinomycosis</i> .
Naso-pharynx ..	Streptococcus, staphylococcus, pneumococcus, <i>B. diphtheriæ</i> , and diphtheroid bacilli, <i>M. catarrhalis</i> , etc.
Larynx and trachea ..	Pneumococcus, <i>M. catarrhalis</i> , and <i>M. paratetragenus</i> , streptococcus, <i>B. influenzæ</i> , <i>B. diphtheriæ</i> , staphylococcus, <i>B. tuberculosis</i> .
Hay fever	Pollen toxins.

PRELIMINARY CONSIDERATIONS.

Excluding the diseases of the external auditory meatus, it appears from the above that for all practical purposes the same bacteria may be said to be capable of initiating processes of disease in each and every region of the ear, nose, and throat. The reason for this is not hard to find, but lies in the fact that an infection of the nose or post-

nasal space is nearly always the primary one, other parts being secondarily infected by direct extension of the process. At times certainly, an infection of the middle ear or mastoid cells is carried thither by the blood-stream from some other focus than one resident in the nose or naso-pharynx ; as, for instance, in otitis media due to the *B. typhosus*. Direct extension is, however, I think, even more common than it is usually regarded to be. It thus follows that in all infections of these parts the first essential to a complete and permanent cure is the establishment of a perfectly healthy condition of the nose and naso-pharynx, and especially of the gums and tonsils. All abnormalities of these parts must therefore receive careful attention at the surgeon's hands, spurs and deflections must be removed, adequate airway secured, infected tonsils be removed, and pyorrhœa alveolaris be adequately treated. In very acute and serious conditions time and opportunity for these performances may be lacking, but so soon as temporary cure has been brought about, strict attention to these points is essential if recurrences are to be obviated. In addition, such measures as clinical experience indicates as being advisable should be taken in regard to the condition in hand ; such as drainage of accumulations of pus, curettage of diseased bone or thickened fibrous tissues, and the topical application of antiseptics.

DISEASES OF THE EXTERNAL AUDITORY MEATUS.

These usually clear up without the necessity of having resort to vaccine treatment ; but in a few infections, such as recurrent boils and chronic eczema, resort may be made to it with great advantage.

Furunculosis, like boils elsewhere, is due to a staphylococcus, usually the *S. aureus*, and treatment is precisely similar to that already described (see p. 145).

Eczema of the external auditory meatus sometimes proves exceedingly refractory to ordinary forms of treatment. The staphylococcus or streptococcus is usually responsible for the condition, occasionally the *B. coli*; while if it be of a moist description, numerous secondary invaders may make their appearance. Among these are diphtheroid bacilli. The significance of these has not yet been determined. Possibly they are often merely harmless saprophytes.

Warner¹ has described one case in which there was a copious discharge of pus and serum. The infection was found to be due to the *B. coli*. An autogenous vaccine was given by the mouth at intervals of a week. After the first dose the discharge appeared to be unaltered, but the irritation was decidedly less. After the second dose the discharge was very much less and the irritation had ceased. By the end of the fourth week there was no discharge, and the ear, though slightly red, caused no discomfort. There was no subsequent recurrence of the eczema.

Cases due to the staphylococcus or streptococcus are sometimes very difficult to cure by local applications, but yield with great readiness to vaccines. Doses of 100,000,000 to 250,000,000 of the former organism, and 25,000,000 to 50,000,000 of the latter may be given at weekly intervals.

¹ Proceedings of the Royal Society of Medicine, October, 1910, Supplement, p. 183.

DISEASE OF THE INTERNAL EAR AND MASTOID CELLS.

Bacteriology.—Owing to insufficient care in differentiation of the pneumococcus and streptococcus by the older investigators, the view formerly prevailed that the pneumococcus was much the most common cause of all inflammatory conditions of the middle and inner ear, and of the mastoid cells. This is now known to be incorrect. In all forms, both acute and chronic, and especially in those complicated by sinus thrombosis, meningitis, and generalized blood infection, the bacterium most commonly found is the streptococcus, either the *mucosus capsulatus* or the *pyogenes longus* variety. Thus, collating the observations of Libmann, Suepffe, Deuch, Wittmank, and others in several hundred cases, it would appear that the streptococcus is responsible for between 65 and 75 per cent. of all cases. Next in frequency come in order the pneumococcus, staphylococcus, and *B. pyocyaneus*. Other organisms, such as the *B. influenza*, *B. coli*, *B. typhosus*, *B. proteus*, diphtheroid bacilli, *M. catarrhalis*, and meningococcus, are occasionally found. The stage of the attack and the site of the lesion are not without influence on the bacteriology. Thus in acute attacks the infection is usually set up by a single organism, rarely by two associated together; in chronic forms mixed infections are the rule. The streptococcus and pneumococcus generally occur alone, while the staphylococcus is usually associated with some other organism, commonly the *B. pyocyaneus*.

Infections of the inner ear and mastoid cells are more likely to be due to a single organism than are those of the middle ear, while sinus thrombosis, meningitis, brain abscess, and generalized blood infections are rarely due

to more than one organism. Thus Libmann¹ has made the following observations: Out of 13 cases of sinus thrombosis investigated, he found the streptococcus in 10 instances, no organism being recovered in the other 3; in 24 cases of meningitis he found a streptococcus in 17, pneumococcus in 4, *B. ps.-influenzæ* in 1, *B. coli* in 1, *B. tuberculosis* in 1. In 5 cases of brain abscess he found the streptococcus in 3, *B. coli* in 1, *B. proteus* in 1. In 55 cases he made blood-cultures; 22 of these yielded a growth, in every instance of the streptococcus; 16 of these cases died and 6 recovered.

In view of the large number of bacteria which are capable of setting up these various conditions, it is obviously necessary that great care must be taken in establishing the correct bacteriological diagnosis, and to this end it will be found advisable to combine blood-cultures with examinations of the local secretion. It is also well to bear in mind that fresh infections are especially liable to be superimposed on primary ones, especially when the condition is a chronic one. Relapse or failure to improve beyond a certain point should at once suggest the possibility of this occurrence, and indicates the necessity for a reinvestigation of the bacterial flora.

Vaccine Treatment.—The best accounts of the vaccine treatment of otitis media are those by Nagle,² Christie,³ Conner,⁴ and Kopetzky.⁵

Nagle employed vaccines in 40 cases. In 6 of these the discharge had been present for only several months, but had resisted all the usual methods of treatment. In

¹ *Archives of Otology*, 1908, p. 22.

² *Laryngoscope*, 1911, p. 48.

³ *Journal of American Medical Association*, 1910, p. 705.

⁴ *Archives of Otology*, 1908, p. 564.

⁵ *New York Medical Journal*, October 15, 1910, p. 763.

the other 34 cases the discharge had persisted for periods varying between one and forty years. The initial dosages were 150,000,000 staphylococci, and 25,000,000 of other organisms. These were repeated or increased at intervals of about three days. In only one case did she fail to bring about ultimate cure, but treatment had to be continued in some cases for a very long time, even one year and nine months. After the ear was dry, a further six inoculations were usually given.

Christie treated 18 cases in all, some being acute, some chronic. In 16 of these the result was completely successful; the 2 exceptions, of eighteen months and two years' standing respectively, were complicated by bone necrosis. All other treatment was stopped when vaccines were begun, but the author admits that the combined treatment—vaccine and local—is obviously the better procedure. Six cases are reported in detail; 3 of these were due to *B. pyocyaneus*, 1 to *Streptococcus mucosa capsulatus*, 1 to *Staphylococcus albus*, and 1 to *S. aureus*. They were of the following standing: Three days (upon old trouble of twenty-six years' duration), a few days, fortnight, fortnight, two months, six months. The initial dose in each instance was 125,000,000, and was increased subsequently to 250,000,000. If no reaction was obtained, the dose was repeated in five days, otherwise intervals of seven to ten days were employed. In each case recovery was complete in less than two months, and no recurrence was experienced.

The following is a short abstract of Conner's treatment and results in the cases of four infants and two young children. In the first case, aged fifteen months, otitis supervened upon pneumonia. After a month's irrigation treatment had failed to cure, autogenous streptococcus

vaccine was given in dosages ranging from 10,000,000 to 25,000,000. Cure resulted in three months. The second case was aged only four days, and was also affected by ophthalmia neonatorum of a malignant type. Bacillus of Friedländer was isolated from the right ear. A dose of 10,000,000 produced decided improvement in six days, but the left ear was found to be also discharging, and here the *S. aureus* was found. Weekly administrations of staphylococcal vaccine in doses ranging from 50,000,000 to 200,000,000, and of bacillus of Friedländer vaccine, in doses of 25,000,000 to 50,000,000, were given. At the end of four weeks there was certainly improvement, and at the end of eight weeks there was no longer any discharge. The baby, however, only weighed 5 pounds, and soon died.

In the third case, aged ten months, otitis supervened on scarlet fever. *S. aureus* was found, and a vaccine given in weekly doses of 50,000,000 to 500,000,000 produced improvement but not cure.

The fourth case, aged seventeen months, was in a miserable condition when admitted to hospital. Seven months' local treatment did not produce much improvement, so treatment was begun with a mixed autogenous vaccine of *S. albus* and *S. aureus* in 100,000,000 dosages at intervals of five to seven days. The dosage was gradually increased to 500,000,000. In about a month apparent cure was brought about, but although the vaccine was continued for another two months, relapse occurred later.

The fifth case was aged five years, and had already suffered from enteric, mumps, diphtheria, scarlet fever, and chicken-pox. Cultures showed pneumococcus and *B. diphtheriæ*. Pneumococcal vaccine in 10,000,000 to

50,000,000 doses and *B. diphtheriæ* vaccine in doses of 5,000,000 to 50,000,000 doses were given weekly. In three months the discharge ceased.

The sixth case was aged two and a half years. Streptococci and *S. aureus* were found in the discharge. Doses of 100,000,000 to 500,000,000 staphylococci and 10,000,000 to 50,000,000 streptococci were given at intervals of five to seven days for three months, when the condition was still uncured.

Conner concludes that these results are not very brilliant, but inasmuch as they were very unpromising cases, better results may be anticipated in private cases in good surroundings. In several acute mastoid cases, upon which simple mastoid operations had been done, he also used vaccines during the post-operative period, but without striking results. One case, due to the streptococcus, in which discharge persisted after operation, however, recovered in five weeks after a vaccine was begun in 10,000,000 doses; another similar case, due to the *Staphylococcus albus*, likewise recovered in two weeks. He also treated two cases of epidural abscess, which did not spontaneously heal well within six weeks. The one due to *M. catarrhalis* healed completely after three inoculations; the other, due to streptococcus and *Staphylococcus aureus*, did not heal completely in three months, but that the vaccine was not without effect was evidenced by the fact that rapid retrogression occurred when its administration was discontinued.

In chronic mastoid cases he secured the best results. Three cases are described fully. The first was a double case in a boy aged six years. After three months' ineffectual local treatment an operation was performed on one side, but eleven months later discharge and fœtor

were still present. The *B. pyocyaneus* was isolated, and 100,000,000 of the autogenous vaccine given. In four days the discharge and fœtor were much reduced, and in four weeks the side which had been already operated on was quite well. The other mastoid was operated on later, and did unexpectedly well—a result which he thinks was due to the prior course of vaccine. The second case, aged two years, had been in hospital practically from birth. The discharge began on both sides at the age of two months. A meato-mastoid operation was done on one side, but seven weeks later there was still some discharge and considerable fœtor. *B. coli* was isolated and inoculations begun with 10,000,000 of the autogenous vaccine. This soon cleared out the *B. coli*, but *Staphylococcus aureus*, bacillus of Friedländer, and *B. pyocyaneus* appeared in turn, and necessitated fresh vaccines. Great improvement was produced on the operated side, but little on the other.

In the third case, aged three and a half years, the general condition was very bad indeed. The double operation was performed. Vaccine treatment was begun with a dosage of 12,000,000 streptococci; later it required supplementing with fresh vaccines of *Staphylococcus aureus* and *albus*. Ultimate dosages of 100,000,000 streptococci, 1,000,000,000 *S. aureus*, and 300,000,000 *S. albus* were attained. At the end of a year's treatment there was no discharge from the right mastoid and very little from the left one.

Conner's conclusions are as follows :

1. Vaccine treatment is not a method available for routine or general use in the chronic suppurative diseases of the ear.

2. Those cases in which free drainage has been estab-

lished by operative measures are the most likely to receive benefit.

3. Benefit may be obtained in some intractable cases which resist all other means of treatment.

4. Secondary operations may sometimes be thereby avoided.

Kopetzky treated 11 cases, 5 being due to the *B. pyocyaneus*, 4 to staphylococcus, and 2 to both these organisms. In 6 of these cases there was evidence of bone necrosis or caries in the tympanic cavity or its annexa. In these the treatment was practically a failure. In the other 5 the trouble was a simple suppurative inflammation of the lining membrane of the tympanic cavity. Four of these were cured, and 1 was improved. In one of these cases three doses of 25,000,000 of a *B. pyocyaneus* vaccine sufficed to produce complete closure of a large perforation, although no other treatment was adopted. Kopetzky believes that the use of vaccines in acute otitis, when the attack is beginning to subside, greatly hastens the process of cure.

Graef and Wynkoop¹ describe a case of especial interest. Widespread necrosis of the mastoid bone and much pus, not only in the cells, but also oozing from the thrombosed lateral sinus, were found at operation. The wound was packed in the usual way. Three days later tenderness developed along the jugular vein, but as the patient had contracted a severe attack of appendicitis, which necessitated operation, the jugular vein was not excised. Streptococci were obtained later in blood-cultures, and a stock vaccine was at once utilized, 15,000,000 being administered on each of three days, after which the autogenous vaccine was substituted, at first in 10,000,000

¹ *New York Medical Journal*, July 9, 1910.

dosages, later in daily increments of 3,000,000, till a maximum of 25,000,000 was attained, when the administration was continued only twice weekly. Altogether twenty-three inoculations were given. The patient made a good recovery, and was discharged on the fifty-sixth day after admission.

DISEASES OF THE NOSE, ANTRUM, AND ASSOCIATED SINUSES.

These may be conveniently subdivided into—

1. Catarrhal rhinitis (acute and chronic).
2. Purulent rhinitis (acute and chronic).
3. Infections of the antrum and associated sinuses.
4. Rhinoscleroma.
5. Lupus.
6. Leprosy.
7. Actinomycosis.

1. CATARRHAL RHINITIS.

Bacteriology.—The organisms capable of setting up catarrhal infections of the nose are the *B. septus* or *Coryzæ segmentosus*, *B. influenzae*, *M. catarrhalis*, *M. paratetragenus*, pneumococcus, bacillus of Friedländer, probably the streptococcus, and possibly the staphylococcus.¹ These may occur alone or in varying combinations. One striking feature about the bacteriology of this condition is the way in which one or other of the above organisms acquires a periodic virulence. For one or more years only certain members of the group are en-

¹ For a description of these organisms, and discussion of their ætiological significance, see the author's 'Bacterial Diseases of Respiration.' H. K. Lewis.

countered ; these then appear to lose all virulence, and completely disappear from the scene, other organisms in turn acquiring the necessary virulence, and initiating a series of epidemics. Thus, for a year or two the *B. septus* and *M. catarrhalis*, alone or in combination, may be responsible for practically all the cases of acute rhinitis that are encountered. Then, for the next year or two, the pneumococcus and *B. influenzae*, alone or in combination, are found in every instance, and so on. The organism most persistently found is the *M. catarrhalis* ; but this organism is a more or less normal inhabitant of the respiratory tract, and especially of the parts other than those of the nasal cavities, and probably acquires a marked pathogenicity only at intervals. In order to determine the precise bacteriology in any given case, smears should be carefully taken through a nasal speculum from the mucous surfaces of the septum and middle turbinate bones, and plates of blood-agar be inoculated therefrom.

Preliminary Considerations.—These are concerned rather with the prevention of future attacks than with the cure of an existent acute attack. In chronic attacks they are of great importance. All abnormalities of the nose and throat should receive the surgeon's care, and pyorrhœa be adequately dealt with by a competent dentist. Adequate airway must be secured, and proper methods of respiration taught. A nasal douching night and morning, with a suitable mildly antiseptic solution—and for this purpose there is nothing to equal glycothymoline—will do much to clear away the accumulated filth laden with bacteria which have been caught up from the air, and to prevent reinfection of the passages. If douches be employed, it is, however, very necessary to warn the patient

against too strong expulsive efforts. The nose should be blown gently, or dissolved mucus and its bacterial content may be driven into the Eustachian tubes, and lead to their infection.

Vaccine Treatment.—This may be begun at any stage of an *acute* catarrhal rhinitis. The sooner the better, as thereby an attack may be shortened and extension to other parts prevented. As soon, therefore, as occasion offers, a dose of stock vaccine should be administered, and cultivations taken to determine the exact nature of the infection, and facilitate the preparation of an autogenous vaccine, should this be required. A very convenient stock vaccine for immediate use is the combined vaccine for colds of the Wimpole Institute, a suitable dose being the 50,000,000 strength. Inasmuch as the immediate effect is a temporary lowering of the resisting powers, it is inadvisable ever to administer such a vaccine until the patient is either on the homeward way or actually in bed. The resultant negative phase does not last more than eight to twelve hours, so that by the following morning a definite rise in immunity has already occurred. Four days later this dosage may be repeated if the patient has reacted to the former dose by definite clinical improvement, slight rise of temperature, malaise, or headache. If no such reaction has been obtained, a double dosage of the stock vaccine may be given. If, however, the autogenous vaccine is then available, it may be used in the following dosages: Pneumococcus, streptococcus, *M. catarrhalis*, *M. paratetragenus*, 50,000,000; *B. influenza*, *B. septus*, and bacillus of Friedländer, 100,000,000. A mixed vaccine does not necessitate any reduction of dosage in the individual components. Four or five days later a double dosage may

be used if the clinical condition indicates the necessity for reinoculation. Thereafter seven-day intervals should be employed.

There is no doubt whatever that the vaccine treatment of acute nasal catarrhs is productive of great benefit in several directions. Thus the attack may be aborted altogether or greatly shortened in duration ; the danger of complications, such as infections of the accessory sinuses and of downward extension into the bronchi and pulmonary cells is considerably minimized ; and the risk of chronicity may be done away with altogether.

The specific treatment of *chronic* nasal catarrhs differs little from that of *acute* attacks. It is especially important, however, firstly, to satisfy oneself that the accessory sinuses are not involved, or if they be, to secure adequate surgical and general treatment of these parts prior to undertaking an expensive and, perchance, needless course of vaccine treatment ; and secondly, to remember that periodic bacteriological examinations should be used to check the progress of immunization, and to give evidence of any possibly newly-acquired infection. It should be hardly necessary to point out that inoculation with a vaccine of *B. influenzae* or bacillus of Friedländer is not capable of preventing the advent of the pneumococcus or *B. septus*, and that such an occurrence would lead to the creation of a totally false impression as to the progress of immunization. But experience has shown me that neglect of these precautions causes the general practitioner more trouble and disappointment than all other causes put together. An autogenous vaccine should be procured for the treatment of a chronic nasal catarrh whenever possible, and the same initial dosages may be employed as for an acute attack, and intervals

of about seven days are most convenient. If progress is not satisfactory with small dosages, resort should be made to larger and larger ones, but so long as either steady or slow progress is being made, or the patient is reacting generally by rise of temperature of 1° to 1.5° F., quickening of the pulse-rate by 10 to 20 beats, slight headache, lassitude, or malaise, it is inadvisable to make any increase in dosage. The most difficult infection to eradicate is certainly that by the *B. influenzae*, next, occasionally, one by the bacillus of Friedländer group. The highest ultimate dosages that I have ever had to employ have been *B. influenzae*, 2,000,000,000 ; bacillus of Friedländer and *M. catarrhalis*, 1,000,000,000 ; pneumococcus, streptococcus, *B. septus*, and *M. paratetragenus* 500,000,000, and in a very extensive experience of this affection I have only encountered two, or perhaps three, cases in which the employment of adequate dosages failed to bring about extinction of the bacterial infection. When accessory sinuses are involved, it becomes a much more difficult task, and success depends largely upon the results secured by surgical, general, and specific treatment with regard to the sinusitis. This question is more fully dealt with in Section 3, p. 343.

Specific Immunization against Acute Catarrhs.—As the specific treatment of catarrhs, both acute and chronic, has been amply demonstrated to be attended with almost universal and complete success, the question at once arises whether nothing can be done along similar lines to secure immunity against future attacks. The success which is now well recognized to attend on such efforts is sufficient answer to those opponents of vaccine therapy who derided my first endeavours and suggestions to this end.

The immunity which may be secured, though high in degree, unfortunately does not last very long, except in a minority of cases. I have had, however, a fair number of cases in which complete immunity has persisted for several years. Among these may be mentioned: (1) A male, aged eighty-four, who fell a victim to three or four attacks of severe nasal and bronchial catarrh every year, each confining him to bed or his room for two to six weeks. He received his last inoculation two years ago, and has not had a single attack since. (2) A male, aged about forty, who could not remember when he had been free from a cold. Last inoculation two and a half years ago. Complete immunity since. (3) A female, aged about forty, who similarly could not remember when she had been free from a chronic cold, and had numerous acute exacerbations every year. No recurrence for over two years. (4) A male, aged thirty-five, complete immunity for two years. These, however, are exceptions, not illustrations of the general rule; and so far as I can estimate, full immunity appears to be maintained in the great majority of cases for a period of about six months. Inasmuch as most countries seem to be visited by two severe epidemics of catarrh every year, which always make their appearance at about the same times, which for England are the months of October and February, the best procedure is either to await the first signs of such an epidemic, or to endeavour to anticipate it altogether, and to subject all such as are unduly susceptible to a short course of preventive inoculations. If the former alternative be selected, it may be possible to make choice of the vaccine or vaccines corresponding to the prevailing infection. If the latter alternative be taken, it will be necessary to employ a very polyvalent

vaccine, the best available being my Combined Vaccine for Colds. The procedure will then be, each September and January, to begin treatment with the combined vaccine, using the 100,000,000 dose for adults, the 50,000,000 dose for children. Seven to ten days later the 250,000,000 and 100,000,000 dose respectively may be given. If a marked constitutional reaction is produced, this dosage should be repeated after another seven to ten days; if no marked reaction ensues, the final dosage should be the 500,000,000 dose for adults, the 250,000,000 dose for children. In by far the greater proportion of cases adequate immunity will be thereby secured. Occasionally failure will result, owing either to extraordinary susceptibility on the part of the individual, or to a defect on the part of the vaccine, which, despite its very high polyvalency, may yet fail to contain the appropriate strain of organism. In all such cases bacteriological examination should be made of the secretion, and an autogenous vaccine prepared to serve both for treatment of that attack and as an immunizing agent in the future.

The efficacy of therapeutic immunization against catarrhs is attested by numerous such occurrences as the following: On several occasions there have been two or three phthisical patients of mine resident in sanatoria swept by epidemics of colds. Of all the residents my patients have alone escaped the epidemics. This can hardly be attributed to any other fact than that they had been systematically immunized against the catarrhal organisms. The same result has been noticed with school-children. Thus, Dr. F. M. Sandwith informs me that he immunized his children with a vaccine which I prepared for them. Some time after an epidemic occurred at their school, but, despite the fact that they

had previously been very susceptible subjects, they escaped infection, and appeared to be the only children to do so. The fact that so many different bacteria are capable of initiating epidemics of colds would seem to militate against this immunizing procedure. Theoretically, it is a strong objection; practically, it would appear to be much less weighty, as no harm would appear to result from the use of such highly polyvalent vaccines, the main fear being that the polyvalency may not be sufficiently great to provide against infection. None the less, the following alternative may be preferred by some: A careful study of the history of past attacks incurred by any given individual will often enable one to form a very good idea whether susceptibility exists towards one or several of the catarrhal groups, and as to which these bacteria may be.¹ Therapeutic immunization may then be performed with a vaccine of the organism, or organisms, to which alone the particular individual appears to be susceptible. In most instances this procedure gives very satisfactory results, but in some it results in considerable disappointment, the patient falling victim to the very next epidemic which, as ill luck may have it, proves to be due to an organism by which he has never previously been attacked.

As we shall see later, immunization against the catarrhal organisms forms a very important part of the treatment of those affected with pulmonary tuberculosis.

2. PURULENT RHINITIS.

(a) *Acute Purulent Rhinitis.*

Bacteriology.—This condition is frequently encountered during the course of such acute specific infections as

¹ Vide 'Bacterial Diseases of Respiration,' p. 71.

scarlet fever, diphtheria, and measles, or as a sequela. Occasionally it is set up as a post-operative infection. The bacteria most commonly concerned are therefore streptococcus, staphylococcus, *B. diphtheriae*, and diphtheroid bacilli.

Vaccine Treatment.—This is conducted on lines similar to those employed in pyogenic infections of the skin and subcutaneous tissues elsewhere. Kolmer and Weston¹ report on 100 cases of scarlatinal rhinitis, in which vaccines of streptococcus, staphylococcus, and diphtheroid bacilli were employed. They concluded that a distinct shortening of the duration of treatment was produced thereby. Graef and Wynkoop² report a case in which a pyogenic infection by the streptococcus, supervening upon a submucous resection for chronic nasal catarrh and ethmoiditis, progressed to a typical meningitis. Streptococci were obtained in cultures from the nose and cerebro-spinal fluid. An autogenous vaccine was administered in daily doses of 10,000,000 for five days, then a daily increase of 3,000,000 was made till the dosage reached 25,000,000. This was given daily for five days, then twice a week, till seventeen doses altogether had been given. An immediate fall in the temperature, previously 104° F., and improvement in the general condition was brought about by the first inoculation, and the patient was discharged perfectly well thirty-eight days after admission.

(b) *Chronic Purulent Rhinitis.*

The most important forms of chronic purulent rhinitis are—(1) That associated with empyema of the antrum

¹ *American Journal of Medical Science*, September, 1911.

² *New York Medical Journal*, July 9, 1910.

of Highmore, or accessory sinuses, for which see Section 3 : (2) that known as ozæna or atrophic rhinitis.

Ozæna or Atrophic Rhinitis.

Bacteriology.—Abel made a careful study of the bacteriology of 100 cases of ozæna, and recovered from each of them a bacterium belonging to the bacillus of Friedländer group. Not only did he find this organism in all these cases, but he found it in no other pathological condition of the nose. Its specificity was further confirmed by the result obtained on inoculating the mucosa of a healthy human nose with a living culture, as thereby an atrophic condition was initiated. It is a non-motile, capsulated, non-Gram-staining bacillus. On agar, it forms a colourless, sticky growth, which is so moist that it runs down to the bottom of the slope. It lacks the iridescence characteristic of the bacillus of Friedländer. On gelatine it forms a similar growth without liquefaction of the medium. In peptone water it forms no indol. In litmus milk it forms slight acid, but no clot. On the various sugar media its fermentative powers are much slower and less than those of the bacillus of Friedländer. In mannite and dextrose it forms acid and a little gas in twenty-four hours ; in maltose and raffinose in forty-eight hours ; in adonite, dextrin, saccharose, and sorbite within seventy-two hours ; in lactose not till the fourth or fifth day ; and not at all in dulcite or inulin.

When inoculated subcutaneously into mice, it proves fatal, as also in about 50 per cent. of guinea-pigs, when introduced into the peritoneal cavity. Subcutaneously in the latter animals it produces no lesion.

Vaccine Treatment. — Page¹ employed autogenous

¹ *Journal of Medical Research*, July, 1912.

vaccines of this organism in two cases of ozæna, but gives no details of the dosage. In the first case he inoculated every three days, and obtained distinct reactions. The patient noted continued subjective improvement, with diminution of crust formation and increased moistness of the secretion. As the right frontal sinus was involved, rapid cure was not to be expected; but after three months of vaccine and no other treatment, great improvement had resulted.

The second case was one of twenty-five years' standing. *B. pyocyaneus*, streptococcus, and *Staphylococcus candidus* were also present in the secretion, in addition to the *B. Ozænæ*. Vaccines of the former two organisms were employed in conjunction after four inoculations had been given of a vaccine of the *B. Ozænæ* alone. Intervals of a week were being used, and at the time of the report the patient was still under treatment. So far the fœtor had been diminished, the discharge lessened and rendered moister, and the nose and throat rendered less dry.

Skillern and Burvill Holmes also report considerable improvement in two cases from the use of a vaccine of the *B. Ozænæ*, while Mosher and Kerr¹ treated ten cases with mixed *Staphylococcus albus*, *aureus*, and *citreus* vaccine, and state that they were all improved and some cured, a marked effect being produced on the headache, fœtor, crusts, and dryness of the mucosæ of the nose and throat. This result may be due to the fact that they employed a vaccine of what are the most common secondary invaders to the *B. Ozænæ*.

Cobb and Nagle² also find that vaccines of the

¹ *Boston Medical and Surgical Journal*, 1909, p. 646.

² *Annals of Otology, Rhinology, and Laryngology*, St. Louis, 1912, vol. xxi.

B. Ozteneæ are of decided value in the treatment of this disease.

As regards dosage, this may be 50,000,000 to commence with, but should be steadily increased till at least 500,000,000 is being administered. Intervals of a week will probably be found suitable.

3. INFECTIONS OF THE ANTRUM AND ACCESSORY SINUSES.

*Bacteriology.*¹—This depends on several factors, chief among which are—(1) Duration of the disease ; (2) nature of the catarrhal epidemic prevalent both at the time when the sinus became involved and at the time of investigation ; (3) site of the infection.

It is probable that the antrum may become infected either via the nose or via a tooth-socket, but the latter route is not only much less common than the former, but also much less common than it is usually regarded to be. The proportion of cases of acute nasal catarrh in which involvement occurs of the antrum or accessory sinuses is probably very large indeed, but in the great majority of instances spontaneous cure is speedily brought about. In a certain percentage, however, infection persists, and the bacteriology then corresponds to that obtaining in the nose itself. As chronicity is established, the more purely catarrhal organisms may become supplanted by the more purely pyogenic ones, and the condition then established in cases of multiple sinusitis may vary in each sinus ; thus the antrum may be infected by the pneumococcus and *B. influenzae*, the ethmoidal cells by the streptococcus, and the frontal cells by the staphylococcus.

Before undertaking the vaccine treatment of these

¹ For a full discussion see 'Bacterial Diseases of Respiration,' pp. 47-50.

cases, it is therefore highly essential to make a thorough bacteriological examination, not only of the nasal secretion, but of that present in each and every one of the infected sinuses. It should also be remembered that mixed infections are the rule and not the exception. It is to ignorance of these facts and insufficient care in establishing the correct bacteriological diagnosis that most of the failures in the vaccine treatment of these conditions is to be attributed. The vaccine treatment should here, more than in any other infection whatsoever, be in the hands of a skilled clinical pathologist, and not in those of a surgeon ignorant of bacteriology.

The most common invaders are the *B. influenzae*, pneumococcus, streptococcus, and staphylococcus. The *M. catarrhalis*, bacillus of Friedländer, *B. proteus*, *B. pyocyaneus*, *B. coli*, and diphtheroid bacilli, may also be found. These may either occur singly or in almost any combination.

Preliminary Considerations.—Some of these have been already referred to under the bacteriology, but in view of their exceeding importance may be again referred to. Firstly, we have the great frequency with which acute catarrhal infections of the sinuses spontaneously recover; secondly, the fact that the infective agent in one cavity may not correspond to that in another; thirdly, that mixed infections are the rule. In addition, it is necessary to recognize that—(1) Acute infections usually respond well to irrigation treatment; (2) in chronic infections it is here, as elsewhere, useless to employ vaccines until free drainage has been established; (3) all predisposing causes, such as enlarged turbinate bones, deflected septum, polypi, and infected tooth-sockets, should first receive attention; (4) the nature of the infective agent, or agents,

is peculiarly liable to undergo change; a fresh infection may at any time be superimposed, especially if a fresh attack of nasal catarrh be incurred; (5) the blood-supply to the parts is poor, so that the antibodies must be considerably increased; high ultimate dosages are necessary; treatment must be prolonged.

Vaccine Treatment.—Inasmuch as acute infections of the sinuses either as a rule get well of themselves, or speedily respond to irrigation with suitable antiseptics, it follows that vaccine treatment will prove most useful in the subacute and chronic stages, when, as we have seen, it may prove helpful to appropriate local treatment. No adequate account by one skilled in vaccine treatment has, so far as I know, been yet published of the results obtained in a series of such cases. My own experience is limited to about half a dozen cases, treated by myself, and about twenty-four cases treated by their own medical attendants. Of my own cases, all but one were very chronic, and had been subjected to operation and general surgical treatment for years. In none of these have I succeeded, even after two years' treatment, in producing such complete cure that vaccine treatment could be altogether discontinued. What has been achieved is—(1) Great diminution of the secretion, perhaps to such a degree that the performance of lavage once every two or three days, by the patient himself, has sufficed to maintain a practically complete absence of pus formation; (2) total disappearance of exacerbations and of recurrent attacks of acute nasal catarrh; (3) considerable improvement in the general health. The best results I have obtained have been in two very chronic cases—one of infection by the bacillus of Friedländer, the other by the *B. coli*. In each of these, operative interference was

refused and could not be insisted on, yet the final result was almost complete cure. A short course of vaccine treatment has, however, had to be continued at four to six monthly intervals. The following initial dosages may be employed : pneumococcus, streptococcus, 25,000,000 ; *M. catarrhalis*, bacillus of Friedländer, *B. proteus*, *B. coli*, *B. pyocyaneus*, or diphtheroid bacilli, 50,000,000 ; staphylococcus and *B. influenzae*, 100,000,000. In the very chronic cases these may have to be increased considerably—perhaps twenty- or even forty-fold—in order to secure the maximum of improvement. The intervals may be between seven and ten days. In subacute forms the same initial dosages and intervals may be employed, and it may be fairly stated that resort should always be made to treatment with autogenous vaccines as soon as the case appears to be hanging fire under the more stereotyped methods of treatment, as thereby a reasonable chance is afforded of prevention of the case drifting into one of chronicity.

4. RHINOSCLEROMA.

Bacteriology.—Although the ætiology of this very distressing complaint is still in dispute, there seems some justification for regarding it as a bacillary infection due probably to the bacillus of Frisch.¹ This organism² is a member of the bacillus of the Friedländer group, but differs from the other members in appearing to be actively motile, and in retaining Gram's stain with some tenacity in sections of the tissues, when these have been hardened in Müller's fluid.

¹ 'Zur Aetiologie des Rhinoscleroms,' *Wien. Med. Woch.*, 1882, p. 32.

² See also Kolle and Wassermann's 'Handbuch der Pathogenen Mikro-organismen,' 1903, Band iii., pp. 414-424.

Some support is given in favour of the ætiological significance of this organism by the fact that a few positive results have been obtained by experimental inoculation of animals, though in the majority of experiments no typical lesions have been produced.

Vaccine Treatment.—Guntzer¹ has reported on two cases treated with a vaccine of Frisch's bacillus after X-ray and other local treatment had failed. In one of these where the nose, glottis, and larynx were all affected, he gave three doses of 250,000,000 at intervals of four or five days. The last of these inoculations produced marked local and general reaction. Subsequently doses of 375,000,000, 500,000,000, and 1,000,000,000 were given and repeated at varying intervals, until forty-three inoculations in all had been given. Although the patient had, at the time of this report, not been cured, he had improved very greatly. The infiltration had retrogressed, there was no longer dyspnœa even on exertion, and he was able to earn his living. This improvement was maintained and continued during the following year, despite the cessation of treatment.

The second case was a very advanced one. The general condition was bad: there was nodular deformity of the nose, the anterior nares were almost closed, and there was infiltration of the upper lip. The tonsils and pillars of the fauces on each side were grown together into a compact mass, and those of the two sides were nearly touching; the naso-pharynx was almost obliterated, and the hard palate was involved. The vaccine was given in doses of 250,000,000 to 1,000,000,000, until thirty-two injections had been given. Local reactions were marked, but at the time of the report the disease had not in any

¹ *Medical Record*, July 24, 1909, p. 129.

way decreased. On the other hand, it had not advanced, and the patient's general condition was very much better. Treatment was being continued, and a year later some definite improvement seems to have resulted therefrom.

5. LUPUS (see p. 164).

6. LEPROSY (see p. 160).

7. ACTINOMYCOSIS (see p. 171).

DISEASES OF THE NASO-PHARYNX.

The two diseases with which we are chiefly concerned here are—(1) Post-nasal catarrh ; (2) diphtheria.

1. POST-NASAL CATARRH.

Bacteriology.—This differs little from that of nasal catarrh except in regard to the relative frequency with which the various bacteria are concerned in the condition. Inasmuch as pyorrhœa alveolaris and follicular tonsillitis are commonly associated with it, or are, indeed, mainly responsible for it, the bacteriology more nearly corresponds to that of these conditions. In other words, mixed infection is the rule, and the bacteria most commonly concerned are the streptococcus, pneumococcus, *M. catarrhalis*, and staphylococcus. Only occasionally does the bacillus of Friedländer or *B. proteus* occur, and in this case the infection is the more likely to be due to a single organism.

Preliminary Considerations.—In view of the close relationship of this disease with pyorrhœa and follicular tonsillitis, it is obviously futile to endeavour to bring about cure by vaccine alone. Strict attention should first be directed to these predisposing causes, to carious teeth, adenoids, and obstructions in the nose. Of local

astringent and antiseptic applications full use should also be made.

Vaccine Treatment.—This is precisely the same as for chronic nasal catarrh, and will present no difficulties. The local condition is a sufficient guide to dosage and intervals.

2. DIPHTHERIA.

Preliminary Considerations.—The increased significance that is now assigned to 'diphtheria carriers' as starting-points for diphtheria epidemics, has caused the vaccine therapy of diphtheria to assume a more important place in the treatment of this disease. Antidiphtheritic serum is a purely antitoxic body, and possesses no bactericidal action, the disappearance of the bacilli being apparently brought about by natural means, of which phagocytosis is probably the most important. As the sequelæ of this disease, such as heart failure and paralysis of the muscles, are probably to be attributed, at least in part, to the persistence of the bacteria in the tissues, it becomes increasingly advisable to insure the extinction of the infection as rapidly as possible. One of the means that has been recently suggested is the daily swabbing and spraying of the parts with living cultures of the *Staphylococcus aureus*, and good results have been reported from this treatment in Germany and America.¹ Personally, I cannot but feel that the method is not devoid of danger to the patient, and think that the use of a vaccine is the much more logical procedure.

Vaccine Treatment.—This should be used, not as a substitute for antitoxic serum in acute cases of diphtheria, but as an adjuvant to it, and should be commenced when

¹ See Bell, *Lancet-Clinic*, August 31, 1912.

solution of the membrane has already occurred, and in all cases where the bacteria are found to persist once convalescence has been established. Although the fact that vaccines have been successfully employed is noticed by several writers, the only account that I can find of an actual case is that reported by Walton Smith.¹ The bacilli were found in the throat of a girl fifteen weeks after antitoxin had been given, recovery being otherwise complete. As staphylococci were also present, a combined vaccine was employed. The first inoculation with 6,000,000 *B. diphtheriæ* and 10,000,000 staphylococcus resulted, within twenty-four hours, in the production of a well-marked reaction at the site of injection, in some general disturbance, and a rise of temperature to 100·2° F. A week later the bacilli were still present, so a second inoculation of 8,000,000 *B. diphtheriæ* was given. The reaction on this occasion was very slight, and subsequent examinations of the throat secretion failed to show the presence of any Klebs-Loeffler bacilli.

DISEASES OF THE LARYNX AND TRACHEA.

The only two affections with which we are here concerned are—(1) Catarrhal laryngitis and tracheitis; (2) tuberculous laryngitis.

1. CATARRHAL LARYNGITIS AND TRACHEITIS.

The bacteriology and vaccine treatment of these conditions are precisely similar to those of bronchitis (see p. 356).

2. TUBERCULOUS LARYNGITIS.

Preliminary Considerations.—Tuberculous laryngitis is nearly always secondary to tuberculous disease of the lungs

¹ *Australian Medical Gazette*, October 20, 1910, p. 543.

or pharynx, the larynx becoming involved in from 15 to 20 per cent. of all cases of pulmonary tuberculosis. Mixed infections are common, and strict attention must be paid to these if any good is to accrue from a course of specific immunization. This especially obtains in pyrexial cases, and in those showing any degree of anæmia. It must be left to the surgeon to decide whether local treatment should be simultaneously applied and resort made to a tracheotomy. Personally I very much favour both procedures in cases that are advanced. In the early non-ulcerated cases trial may first be made of tuberculin alone, provided the patient can be relied upon to maintain strict silence.

Vaccine Treatment.—As we have seen, mixed infection is commonly present in ulcerated cases, the streptococcus, pneumococcus, staphylococcus, and *M. catarrhalis* being the secondary invaders most commonly encountered. An autogenous vaccine of these may be combined with the tuberculin, or, better, I think, given at alternate administrations, which may then be made every five days. Ten million streptococcus, 25,000,000 pneumococcus, 50,000,000 *M. catarrhalis*, 100,000,000 staphylococcus are appropriate initial dosages. As regards the choice of tuberculin, personally I prefer the mixed bacillary emulsions, beginning with 0·00001 c.c., and increasing the dosage by this amount after every two or three administrations, until 0·0001 c.c. is being given, increments of 0·0001 c.c. being then made in a similar manner, after each series of three or four doses, until 0·001 c.c. is being given. This, however, is only a very rough rule. If good progress is being made with small doses, it is very unwise to increase them, and, above all, must careful watch be kept on the pulmonary condition, for it is no uncommon experience to find that

improvement in one part and retrogression in the other may go hand in hand. In private practice I think good results are to be secured in the majority of cases : firstly, because they are usually seen early ; secondly, because they can be kept better under control ; thirdly, because prolonged treatment can usually be given. In hospital cases the outlook is very much more gloomy.

Different authorities advise different preparations of tuberculin, and hold very different views of the prognosis. Von Ruck¹ has recorded 102 cases treated with his watery extract of the tubercle bacillus : 38 of these cases had only slight infiltrations, and all were cured ; 58 had marked infiltrations. Of these 29 were cured, 12 improved, 6 unchanged. In only 2 did ulcers form after the beginning of treatment.

Blumenfeld advises tuberculin only in obstinate cases. He thinks that it alone can do very little in laryngeal tuberculosis, and that the percentage of cures is nearer 5 or 6 per cent. than the 50 or 60 per cent. recorded by some.

Wilkinson, treating his cases as out-patients and with as large doses of P.T.O., P.T., and Old Tuberculin as they can tolerate without responding by marked reactions, gives his results as follows :

Stage.	Total Cases of Phthisis.	Number of Laryngeal Cases.	Cured.	Improved.
1	150	4	4	2
2	90	15	13	
3	?	6	3	

¹ 'A Clinical Study of 337 Cases of Pulmonary Tuberculosis.' 1909.

Some observers state that tuberculous deposits and tumours are not so favourable for specific treatment as ulcers in general, and especially elongated ones of the cords, and that cases of perichondritis of the arytenoids, with swelling of the epiglottis and ary-epiglottic folds, are not improved. Personally, I feel that specific and local treatment should be so invariably combined that it should not be possible to judge of the results of vaccine treatment alone.

HAY FEVER.

Although it is very doubtful whether bacteria and bacteria alone are ever capable of giving rise to the group of symptoms known as 'hay fever,' it is yet advisable to make mention of the most recent form of treatment of this complaint, inasmuch as it is based on principles precisely similar to those which guide us in the treatment of the bacterial diseases.

Ætiology.—There appears to be an instability of the vasomotor centre in the medulla, which is readily affected by afferent impulses from the ocular, nasal, and bronchial mucosæ. The most effective stimuli are those given, as Dunbar has shown, by the toxins contained in the pollen of various grasses and flowers. The treatment of the complaint may therefore follow several lines, such as—(1) Stabilization of the vasomotor centre in the medulla by linear cautery of the nasal mucosa, as Francis has advised; (2) removal of the patient from the influence of toxins of the pollen, when this is floating in the air; (3) raising the immunity of the sufferer to the toxins by means of therapeutic inoculations, according to the principles of vaccine treatment. The last of these is the method to which reference will be made.

Vaccine Treatment.—The first step is to establish a connection between pollen toxin and the attacks of hay fever in any given sufferer. This is done by means of an ophthalmo-reaction, corresponding to Calmette's reaction in cases of infection by the *B. tuberculosis*, as modified and applied by Noon. One gramme of the pollen of *Phleum pratense* is extracted thoroughly with 50 c.c. of water, and for the sake of convenience the extract is arbitrarily assumed to contain 20,000 units of toxin in each cubic centimetre. The following dilutions are prepared from the extract: 5,000, 1,500, 500, 150, 50, 15, and 5 units in each cubic centimetre, this wide range being necessary owing to the extreme variation exhibited by various individuals in their susceptibility to the toxin. Two or three drops of each dilution are put up in glass capillary tubes, and used for the performance of a test upon the ocular conjunctiva in precisely the same manner as a Calmette's test is carried out. The weakest dilution is used upon one eye. If there is no reaction after two or three minutes, the next highest strength is used upon the other eye, and so on with each eye alternately, until a reaction is obtained. Not only is susceptibility thus demonstrated, but the appropriate initial dosage is simultaneously determined, for the appropriate initial dosage for subcutaneous immunization is one-third of a cubic centimetre of the strength which, when applied to the eye, gave a positive reaction. For the treatment of an actual attack one-half the initial immunizing dosage should be used. The subsequent procedure is as follows: (a) For protective purposes the initial dose is repeated in eight days. After a similar interval the next higher dose is given, and so on until immunization is shown to be complete by the fact

that the patient no longer responds to an ophthalmo-test with the 5,000 unit dilution. (*b*) For treatment, the initial dosage, which, as we have seen, is half that appropriate for protective use, is repeated in five days. After a similar interval the next higher dosage is administered, and so on, just as under (*a*).

The elaboration of this highly scientific mode of treatment is of such recent date that it is hardly possible at present to dogmatize about results. So far, however, as can be judged from the results of the past hay-fever season a considerable measure of success is to be anticipated. Many patients have escaped completely, and the greater majority have suffered from nothing beyond very mild attacks.

CHAPTER XII

DISEASES OF THE LOWER RESPIRATORY TRACT

Disease.	Bacteria Concerned.
Bronchitis	Pneumococcus, streptococcus, <i>B. influenza</i> , <i>M. catarrhalis</i> , <i>M. paratetrigenus</i> , bacillus of Friedländer.
Asthma	Streptococcus, <i>M. catarrhalis</i> , pneumococcus, <i>B. influenza</i> , <i>M. paratetrigenus</i> .
Pneumonia and Broncho-pneumonia	Pneumococcus, bacillus of Friedländer, <i>B. influenza</i> , streptococcus, staphylococcus, <i>B. typhosus</i> , <i>B. coli</i> .
Lung abscess and bronchiectasis	As for pneumonia, with the addition of <i>B. pyocyaneus</i> , <i>B. proteus</i> , <i>M. tetragenus</i> .
Whooping-cough . .	<i>B. Bordet-Gengou</i> (primary), <i>B. influenza</i> , pneumococcus, and <i>M. catarrhalis</i> (secondary).
Actinomycosis . . .	<i>Streptothrix actinomycosis</i> .
Phthisis	<i>B. tuberculosis</i> (primary), pneumococcus, streptococcus, staphylococcus, <i>B. influenza</i> , <i>M. catarrhalis</i> , <i>M. tetragenus</i> , <i>M. paratetrigenus</i> , <i>B. coli</i> , <i>B. proteus</i> , bacillus of Friedländer, etc.

A complete discussion of the question of the use of vaccines in diseases of the lower respiratory tract would require an amount of space far in excess of that available here. The essential elements will therefore alone be dealt with, and the reader must be referred to the author's 'Bacterial Diseases of Respiration'¹ for further information on this subject.

¹ London: H. K. Lewis.

BRONCHITIS.

Bacteriology.—Reference to the table at the head of this chapter will show that a considerable variety of bacteria are concerned in the production of each of the bacterial diseases of the lower respiratory tract. The precise determination of the bacteriology in any given condition and in any given case is beset by certain difficulties, chief among which is the element of contamination introduced into the specimen of sputum as it passes from the alveoli or bronchial tubes to its exit from the mouth. Considerable care is therefore requisite in the taking of the sample in order to reduce contamination to a minimum, and a knowledge of the cytology of the sputum, in order to enable a correct conclusion to be formed as to the origin of the portion under examination (for details, see ‘Bacterial Diseases of Respiration’). It must here suffice to say that the following bacteria are certainly capable of initiating a catarrhal condition of the bronchial tubes—viz., pneumococcus, streptococcus, *B. influenzae*, *M. catarrhalis*, *M. paratetragenus*, bacillus of Friedländer. Occasionally the infection is due to a single organism—more often it is due to more than one organism—any of the above occurring in varying combinations. When an acute bronchitis arises as a primary infection, and not as a secondary one to a catarrh of the upper passages, the infection is more likely to be a simple one; but even then is as a rule due to two associated bacteria, such as pneumococcus and *B. influenzae*, or streptococcus and *M. catarrhalis*. It thus follows that autogenous vaccines are likely to prove of more service than stock ones, even if these be highly polyvalent.

Preliminary Considerations.—Bronchitis is a condition pre-eminently suited for vaccine treatment, inasmuch

as the blood-supply to the parts is copious, and ample facilities, as a rule, exist for the removal of secretion as it forms. When the sputum is scanty and difficult of expulsion, there are numerous drugs available for the remedy of these defects. Acute and subacute bronchitis is more responsive to treatment than chronic bronchitis, especially if this be complicated by emphysema and dilatation of the bronchial tubes.

Vaccine Treatment.—Although in the case of some infectious diseases it is quite safe to ignore the production of a 'negative phase,' in diseases of the lower respiratory tract in general, and in bronchitis in particular, the production of a period of lowered resistance, which index observations have shown to occur beyond question, is not without its bearing on the procedure. Thus it is obviously unwise to perform an inoculation in the morning upon an individual who has to go out of doors thereafter and expose himself to possible chill and damp, or to perform it in the afternoon and allow a subsequent outing to dinner and a theatre, with the resultant rapid changes of temperature. Inoculations should therefore be done between 4 and 7 p.m., unless the patient be confined to bed or to the house, and a light dinner and early retirement to bed be enforced.

The control of dosage and intervals in all bacterial diseases of the chest is based upon—(1) Careful systematic stethoscopic examinations of the chest; (2) measurement and bacteriological examinations of the sputum; (3) clinical observation generally of the patient.

It may be laid down as a general rule that no dosage of a vaccine is truly efficient which fails to produce a slight constitutional reaction and a reaction at the focus of infection; and that the most appropriate dosage will

here be one that brings about—(1) A constitutional reaction within twelve hours, characterized by any one or more of the following : A rise of temperature of between 1° and 1.5° F., an acceleration of pulse-rate of 10 to 20 beats, a slight headache or feeling of malaise. These should speedily be replaced, certainly within another twelve hours, by a fall of temperature to normal, or to a lower level than that previously existent in the case of any pyrexia, by a corresponding or greater fall of pulse-rate, or by an increased feeling of general comfort and well-being. (2) A definite focal reaction within twelve hours, characterized by increase of cough and sputum, which latter should, however, be more fluid in consistency, and by apparent extension of the physical signs, moist râles and rhonchi appearing where previously only dry ones were to be heard. These similarly should begin speedily to retrogress, so that within another twelve or eighteen hours the cough should be less troublesome than before, the sputum reduced in quantity and easier of expulsion, and the area and degree of involvement of the tissues likewise diminished.

My experience of the vaccine treatment of diseases of the chest is sufficiently great to justify a certain amount of dogmatism upon this question, and I am absolutely certain that in by far the greater proportion of cases the best results can only be obtained by the use of dosages which will bring about such a cycle of events as those above described, whether the condition be one of bronchitis, asthma, pneumonia, or pulmonary phthisis. A certain amount of judgment must nevertheless be introduced, and if the process be a very acute one, the area of tissues involved great, or the obstruction to the circulation such that undue strain is being thrown upon the

heart musculature, the wiser and safer procedure is to reduce the dosage by one-half or even in a greater ratio, and aim at the production of speedy, if limited, amelioration without any precedent exacerbation of the process.

The initial dosages which I have found to be devoid of all danger are — *Pneumococcus*, streptococcus, 25,000,000 ; *M. catarrhalis*, *M. paratetrigenus*, bacillus of Friedländer, 50,000,000 ; *B. influenzae*, 100,000,000. In acute and subacute cases I have never yet seen these fail to produce some amelioration, and in chronic cases but very rarely. Subsequent dosages and intervals are controlled as follows : If improvement set in within twelve or eighteen hours without any precedent exacerbation (*i.e.*, reaction), employ the double dosage at the first definite signs of retrogression—which will usually occur in between three and five days—unless the improvement be so satisfactory as to negative the advisability of increased dosage. If improvement set in within twenty-four to forty-eight hours of the inoculation, but only after a precedent reaction of twelve to eighteen hours' duration, repeat that dosage at the first definite signs of retrogression. These will usually set in after four to seven days. When complete recovery has apparently occurred, it is well to give a further series of two or three inoculations at intervals of seven to ten days, employing the highest dosage that was finally attained, or even one of double magnitude, as by this procedure the risk of future relapse will be greatly minimized.

In this connection it is well to bear in mind that it matters little how well the patient feels or how free the chest may be from physical signs if sputum be still voided laden, say, with *B. influenzae* or pneumococcus.

The infection is in this case still existent, if more or less dormant. The risk of relapse should be impressed strongly on the patient, and the utmost powers of persuasion exercised in order to secure consent to the prolongation of the treatment.

Results of Vaccine Treatment.—In a disease process varying so greatly as does bronchitis in its severity and duration it is perfectly impossible to adduce statistics which will have the slightest value; all that can be done is to record one's own clinical impressions, and what are, to my mind, of even greater value, in this instance if in no other—viz., the opinions of the patients themselves. Bearing in mind the fact, which I have so often urged, that vaccine treatment does not consist in mere inoculation with bacterial products, but in the combination of this procedure with such measures as clinical experience has indicated to be of definite value, I would be prepared to state that vaccine treatment is of the very greatest value in almost all cases of bronchitis, acute, subacute, or chronic. Personally, I have never seen the case, excluding one or two of advanced emphysema, which did not benefit, speedily and markedly, from the administration of the suitable vaccine in suitable dosages at suitable intervals, and I do not believe that such a case exists. The duration of the attack is reduced, convalescence is shortened, complications obviated, and relapses reduced to a minimum. In many cases the judicious use of immunizing doses at appropriate times of the year will do much to prevent the patient falling victim to fresh infection. The question has been raised whether, in the event of a fresh attack being incurred despite a course of immunization, this attack may not be of aggravated intensity. To this

it is impossible to give a dogmatic answer, but the truth I believe to be this: in the great proportion of such cases the attack is of greatly diminished intensity, but occasionally it would appear to be of increased severity, as the infective agent must have been of very great virulence and gained access in very great numbers in order to have broken down the strengthened barriers. In only two or three instances have I seen occur what may have been an event of this description: actually I believe they were instances of infection by a totally new organism. In one case this was certainly so, and this possibility must always be carefully remembered before a too rapid, and perhaps quite unjust, conclusion is arrived at. Time and close observation, clinical and bacteriological, is necessary before a definite answer can be given to this very important question.

ASTHMA.

Bacteriology.—The warnings that have been given in regard to the determination of the bacteriology of a given case of bronchitis hold with equal and perhaps greater force in regard to the case of asthma. Into many cases of asthma a bacterial element enters, and especially when much bronchial catarrh is coexistent. When asthmatic spirals are present in the sputum, these should be well washed in sterile salt solution, and utilized for bacteriological examination. In all cases it is advisable to employ sputum voided at the height of an attack. When the sputum is scanty, the bacteriology is usually found to be comparatively simple, monorganismal and binorganismal infections being relatively common, the bacterium most commonly present being the streptococcus—especially that variety which I have described and

entitled the *Streptococcus maximus*¹—the pneumococcus and the *M. catarrhalis*. When there is much bronchial catarrh, the bacteriology is more complex, and any combinations of these organisms, and of the *B. influenzae*, *M. paratetragenus*, and bacillus of Friedländer, may be present.

Preliminary Considerations.— Before beginning the treatment of a case of asthma according to any method, careful observations should be made to determine the precise ætiology of the given case. To enter into the various theories of the causation of asthma would be quite outside the scope of this work, but I have seen sufficient of the careful work of Dr. Alexander Francis to be convinced that in many cases the essential condition is an instability of the vasomotor centre in the medulla, an instability which may be disturbed by afferent impulses arriving there from the stomach, heart, lungs, or nose, and especially from the last of these. It thus follows that a stabilizing of the vasomotor centre by delicate electrical cauterization of the sensitive areas in the nasal mucosa is very often an essential preliminary to any attempt at reducing the afferent impulses from the lung, set up by the bacterial toxins which may be there liberated. If the nasal impulses be abrogated, this may alone suffice to stabilize sufficiently the vasomotor centre. Occasionally, however, this is not the case, and the aid of vaccine treatment may be sought to insure further stabilization. Resort should, however, be made to vaccines, only when due attention to all nasal abnormalities, gastric and cardiac derangements, and the general hygiene has failed to bring about the desired result.

¹ See 'Bacterial Diseases of Respiration,' p. 29, and Figs. 6 and 7, Plate II.

Vaccine Treatment.—This should be conducted upon lines similar to those already described under ‘Bronchitis.’ Similar initial dosages should be utilized, and those dosages are to be considered as effective which produce a short and mild, but none the less typical, attack on the evening of administration. On the following days the attacks should be less frequent, less severe, and of shorter duration than previously, and retrogression in any of these directions is the signal for reinoculation.

In cases characterized by profuse expectoration it must be borne in mind by the administrator, who should duly warn the patient accordingly, that as the amount of the expectoration is reduced, the difficulty in its expulsion may be increased, and that it may be necessary to mask improvement by the administration of drugs, which will, for the time being, increase the expectoration. The steering of a case of asthma by the aid of vaccines to a safe harbour, is as difficult a manoeuvre as it is easy in regard to a case of bronchitis; but none the less, in a small percentage of cases vaccine treatment does prove of very great service in the treatment of asthma, and is well worth a trial in cases which have proved refractory to other methods. Actually, in about 25 per cent. of my cases, which have all fallen into this category, I have finally secured almost complete freedom from their attacks, and in about a further 25 per cent. great improvement has been brought about; but although prior measures had apparently failed, I yet feel that they were indispensable preliminary adjuncts to the course of specific therapy, this latter being merely the hammer which dislodged the last wedge, and allowed the vessel of immunity to be launched successfully.

PNEUMONIA.

Bacteriology. — Ample recognition is rapidly being accorded to the fact that typhoid fever, commonly so called, is not an entity, but is a group of diseases due to a number of closely allied organisms; and it has been long recognized that a condition of septicæmia may be set up by a considerable number of different bacteria, and that it is of some importance to ascertain what is the precise organism at work. With regard to pneumonia the case is different. The clinician with any pretence to thorough training is not ignorant of the fact that several bacteria besides the pneumococcus of Fraenkel are capable of initiating the pneumonic process, but of this fact he makes not the slightest use. His mortality rate has settled down to a more or less constant, and if he endeavour to reduce it by the use of vaccines, it is by employing a pneumococcal vaccine in each and every case, regardless of the exact nature of the infective agent. This slipshod method, of use only for the compilation of a paper on the use of vaccines in a series of cases of pneumonia, cannot be too strongly condemned. No medical man is entitled to treat his cases of pneumonia with a stock pneumococcal vaccine without prior determination of the infective agent in each and every case, especially if he intend to record his results for the guidance of others. But it will be urged that almost all cases of pneumonia, and especially of lobar pneumonia, are due to infection by the pneumococcus, and support may be given to this view by some bacteriologists. This, however, is only a partial expression of the truth. The percentage of cases of pneumonia due to the bacillus of Friedländer, strepto-

coecus, staphylococcus, *B. typhosus*, and *B. coli* put together, may be relatively small; but the percentage of cases of pneumonia due to the pneumococcus alone by no means accounts for all the remainder, for a not inconsiderable percentage of all cases is due to a mixed infection by the pneumococcus and *B. influenzae*; and despite the fact that the disease may appear to run the course more or less characteristic of an infection by the pneumococcus alone, the importance of the *B. influenzae* is little, if any, less than that of the pneumococcus. Failure of recognition of this very important fact is one only of the factors which vitiate the observations and conclusions recorded by several on the vaccine treatment of this disease. To a second, consideration will next be given.

Preliminary Considerations.—Once again it becomes necessary to emphasize the fact that the introduction into the tissues of even the appropriate dosages at the appropriate intervals of the appropriate vaccine is not the beginning and end of vaccine treatment. The determination of the advent to the infected focus of the immune bodies elaborated in response to these well-adjusted stimuli is an equally important and essential part of the treatment. In bronchitis there is, as a rule, no obstacle whatsoever to the advent of the antibodies, but in pneumonia the case may be very different, and it becomes necessary to consider in some detail the pathology of this disease. In the *first* stage, that of congestion, the capillaries are dilated and tortuous from distension with blood; the air cells are not as yet completely airless, but are more or less filled with frothy, reddish serum albumin. The supply of opsonin and other antibodies in the circulating fluids is below the

normal, the leucocytes, as a rule, considerably above the normal.

During the *second* stage, known as 'red hepatization,' from the resemblance which the lung then bears to the liver, the organ is of a dull red colour, finely granular in section, completely airless, solid, and sinks in water. The contents of the alveoli consist of coagulated fibrin, which holds in its meshes red blood cells, leucocytes, exfoliated epithelium, and bacteria. Although the capillaries are much compressed, they, for the most part, remain pervious. The supply of antibodies remains low, and the leucocytes in the circulating blood have fallen considerably, although they may still be above the normal. This fall may be due to the vast numbers stored up in the pulmonary tissues.

The stage of red hepatization passes into the *third* stage, that of grey hepatization, the change of colour being brought about by the extravasated red corpuscles losing their hæmoglobin, by the stasis of the circulation through the capillary vessels of the alveoli, and by the increased number of leucocytes which crowd the air cells and alveolar walls. The leucocytes in the blood-stream have now fallen to their minimum.

In cases which pursue a normal course, this stage of grey hepatization so rapidly passes into that of 'resolution,' that it may be regarded as the stage of commencing resolution; the leucocytes and exfoliated epithelium undergo granular and fatty degeneration; the fibrin softens and is absorbed; the capillary circulation becomes actively re-established; the alveoli again contain air, and the alveolar epithelium is regenerated. The commencement of this process of resolution would appear to coincide in point of time with the sudden fall of temperature,

occurring in nearly 50 per cent. of cases, known as the 'crisis,' and with the sudden rise of leucocytes and immune bodies in the general blood-stream. Chart XI. shows well the relationship between temperature, leucocytes, and opsonic index at the various stages of the disease.

CHART XI.



RELATION BETWEEN LEUCOCYTES, OPSONIC INDEX AND TEMPERATURE, IN A CASE OF PNEUMONIA. (Eyre.)

Dotted lines = number of leucocytes per cubic millimetre; thick line = opsonic index; thin line = temperature.

The chief factors concerned in the processes of cure are—(1) Leucocytes; (2) endothelial cells of the alveoli; (3) opsonins; (4) antitoxins, agglutinins, and other immune bodies.

The opsonic index yields a very fair indication of the progress of immunity, and the extinction of the infective agents would appear to depend largely upon the action

of opsonin, which is chiefly of the thermolabile variety. The phagocytosis is not, as might be supposed, carried out in the main by the polymorphonuclear leucocytes, which, as we have seen, have so largely increased in numbers at, or just before, the crisis, but, as De Jong has pointed out, by the endothelial cells of the alveoli, many of which have become transformed into macrophages. The chief rôle of the leucocytes would seem to be the formation and excretion of ferment for the solution of the fibrin filling the alveolar cells. To this end is probably due the great storing up of leucocytes in the pulmonary tissue.

To the poisoning of the nerve centres by the endotoxins liberated on the extracellular death of the pneumococci, the symptoms of rapid respiration, high temperature, and failure of the heart musculature, are to be attributed, and the satisfactory elaboration of the corresponding auto-endotoxin is therefore a very essential factor for recovery, and the production of the crisis is dependent thereon.

Let us now consider what bearing these various facts have upon the application of vaccine treatment to this disease. Our objective must be a twofold one—to kill the bacteria and to neutralize their toxin. The question is, Are these possible of attainment? The answer is, This depends largely on the stage of the disease, the virulence of the infection, and the responsive powers of the individual.

In the stage of pulmonary congestion the bacteria are circulating in the blood-stream, and are present in but scanty numbers in the pulmonary tissues. The resisting power of the body has been obviously broken down, and bacteria circulating in the blood-stream do not

appear to be capable of leading to the elaboration of antibodies ; there is thus both a local and general defect of these, but at the same time the amount of toxin formed is not considerable. If, therefore, the bacteria could be exterminated, the disease process would be ended. It is now well recognized that the introduction into healthy subcutaneous or muscle tissues of a therapeutic dose of vaccine will lead to the speedy elaboration of the corresponding antibodies. A vaccine of pneumococci is but slightly toxic, and its administration leads to the elaboration of considerable amounts of opsonin, which is chiefly of the thermostable variety, and of a small amount of antitoxin. The fact that this is precisely what is then required is the strongest possible argument for the employment of a vaccine at the very inception of the attack. It is true that the virulence of the infection then is high, but so is the responsive power of the individual. Unfortunately, there are two obstacles to this procedure : (1) The fact that the opportunity does not always present itself, many cases not being seen till the disease processes are further advanced ; (2) the refusal of medical men to recognize every case of pneumonia as potentially a fatal one.

When consolidation has occurred, bacteria are still often to be found in the blood-stream, but their multiplication in the pulmonary tissues has much advanced. Here they are enclosed in a meshwork of fibrin, in a warm nidus admirably suited to their growth, the blood and lymph supply being more or less in a state of stasis ; even if the amount of immune bodies in the body generally is more than adequate, these are not available, or only to a limited extent. No immediate material good might therefore be anticipated from increasing them by means

of a therapeutical inoculation. That good does sometimes result therefrom is due to the fact that all portions of the infected lung are not in the same stage : one area may be in a state of congestion, another in that of red hepatization, and yet a third in that of commencing resolution. The main objective, therefore, is to relieve the strain on the heart's musculature as much as possible by lowering the viscosity of the blood with full doses of citric acid, by dilating the blood-vessels locally by the application of heat, etc., and by relieving the general blood-pressure by promoting free diaphoresis and action of the bowels, and, if necessary, by bleeding. At the same time we may increase the amount of antibodies, both antitoxic and antibacterial, and the number of leucocytes against the time when commencing resolution may enable them to be carried to the battle front. Resolution will inevitably entail the free liberation into the re-established circulation of quantities of toxin which have been stored up in the consolidated tissues. Hence it is very important now to insure that the leucocytes and various antibodies can reach the infected areas with the least possible difficulty, and to preserve the heart musculature as much as possible from the action of the bacterial toxins. Were a really reliable antitoxic serum available for the neutralization of the toxins, the combination of serum and vaccine could hardly fail to prove of the utmost value during this period of resolution. Unfortunately, the best available sera, Romer's and Pané's, appear to leave much to be desired ; their defects may, however, be more apparent than real, failures with them being, perhaps, as much due to their improper use—viz., insufficient dosage and non-systemic administration—as to any intrinsic imperfections.

The administration of a vaccine when resolution is impending will prove of immediate service provided that—

1. The supply of antibacterial bodies is otherwise insufficient.

2. The tissues are capable of responding to stimulation, and this they almost invariably are.

3. The heart mechanism is sufficiently strong to withstand the attack of the toxins so copiously liberated during this stage.

As we have seen, the production of the 'crisis' is due to the massive neutralization of toxin by antitoxin. Hence it is that a small dose of vaccine may at one time suffice to produce an immediate reaction, as evidenced by crisis occurring, and at another time may appear to fail. The power of a vaccine to stimulate the formation of antitoxin is but slight; hence, if the defect in antitoxin is small, the addition of a small quantity will suffice; but if the defect be great, a much increased dose of vaccine may fail to produce the additional amount requisite to make good the considerable defect. The total amount of antibody then present being the sum of the amount produced so far by natural means, plus the amounts produced by the inoculation of the vaccine, requires further supplementing, either by the natural response of the body to the infection, or to the stimulation of another dose of vaccine, or by both these means.

As has been already mentioned, when the fall of temperature is by lysis, this massive neutralization of toxin would not appear to occur, and it is worthy of note that the proportion of cases in which 'lysis' occurs rather than 'crisis,' appears to be greater in vaccinated than in unvaccinated cases.

These conclusions may be briefly summarized as follows :

1. The administration of a vaccine in the earliest stages of a pneumonic attack can hardly fail to be productive of good in a very considerable percentage of cases, for thereby is insured the formation of adequate bactericidal bodies, and these are precisely those which are of service at this period of the disease.

2. The administration of a vaccine during the period of consolidation theoretically can hardly be productive of immediate good, but the resultant immune bodies may prove of considerable service once 'resolution' has begun. Owing, however, to the fact that the stage of the disease may vary considerably at different foci, the good resulting from vaccine treatment may be much greater than might be anticipated. I cannot help feeling that these are the cases where the fall of temperature is by 'lysis.'

3. The administration of a vaccine during the period of resolution will prove of service, especially if resolution be delayed, and if the supply of bactericidal bodies be otherwise insufficient.

It must, however, be clearly borne in mind that no vaccine treatment will prove of service unless—

1. The vaccine be the proper one and be properly prepared.

It is no use employing a pneumococcal vaccine in a streptococcal or Friedländer infection, nor is it any use employing a vaccine devoid of immunizing properties. I have already mentioned that some strains of pneumococci yield a good vaccine only when heat is used to insure sterility, others only when sterilized with antiseptic.

Experience has also shown that an autogenous vaccine is preferable to a stock one, but there is much to be said

in favour of beginning treatment immediately with a stock polyvalent vaccine of proved immunizing powers. While some virulent strains of the *B. diphtheriæ* yield the most potent antitoxin, and some strains of the *B. typhosus* of very low virulence the most powerful vaccine, with the pneumococcus the more highly virulent the strain, as a rule, the more potent is the vaccine. The pneumococci isolated from a given case of pneumonia may vary much in virulence amongst themselves. It is, therefore, obvious that in the preparation of an autogenous vaccine cultures should be taken, not from one, but from numerous colonies.

2. That adequate dosage be employed.

Two things that have especially struck me in reading the clinical histories of cases reported by those who have failed to secure satisfactory results have been—

(a) The inadequate dosages. For instance, in the record of nineteen cases by one observer, I find that nine cases did not receive a dose of even 5,000,000, and only one case a dose of 25,000,000. This is little more than playing with vaccine treatment.

(b) The tendency to reduce subsequent dosages when the patient fails to make any response to a first dose, which, in fact, was itself quite an inadequate one, judged by the experience of all those who have achieved good results. Failure to respond in any way to a given dosage is an indication, not for reduced, but for increased, subsequent doses.

I might also add that increased toxæmia has been at times regarded either as a bad effect, or as indication for diminished dosage; in reality it may be neither. It is an indication for promoting neutralization and excretion of the toxins by every available means, and it may also

be indicative of hastening resolution and consequent increased absorption of the toxins into the general circulation; but it certainly is not indicative of postponing further inoculation or of diminishing the dosage. It may be so in the case of some infections, but, above all, this is not the case with pneumococcal infections. The toxic contents of a pneumococcal vaccine are so small that the amount so introduced into healthy tissues is without effect on the circulating mass, and only leads to the elaboration of the corresponding antitoxin, while the stimulus to the formation of opsonin, and so to the phagocytosis of the bacilli and neutralization within the macrophages and polynuclear cells of their endotoxins, is very great. Personally, I have never seen a pneumococcal vaccine do any injury to a patient; *per contra*, I have seen several cases of persistent hyperpyrexia, with low muttering delirium, one or two apparently comatose, make almost immediate response to an inoculation of 25,000,000 or 50,000,000. It is true that these were cases with marked bacteraemia, but this, I think, they often are.

In conclusion, I will briefly summarize the procedure which has been found by most experienced observers to be the best, and give a short résumé of the results they have obtained.

Vaccine Treatment.—1. Take sputum smears and cultures. If in early stage, blood-cultures; if in advanced stage, perform a lung puncture, and proceed to the preparation of an autogenous vaccine.

2. Immediately administer a dose of not less than 25,000,000 of a polyvalent stock vaccine, prepared from virulent strains and of proved immunizing power.

3. If no definite response within thirty-six to forty-

eight hours, repeat the above dose of stock vaccine, or preferably of the autogenous vaccine, if this be ready.

4. If still no response, administer double the above dose in thirty-six to forty-eight hours; if response, as evidenced by improved clinical signs and symptoms and increased well-being of the patient, defer reinoculation for three days, or until the first signs of retrogression in the general condition or clinical signs and symptoms.

5. Maintain dosage or even increase it, and continue inoculations at intervals of three to four days, until the patient is perfectly well.

6. If the patient at any time takes a sudden turn for the worse, make diligent search above all for such complications as may require surgical interference. It may be advisable in such conditions to suspend specific treatment, but immediate reinoculation, perhaps with an increased dosage, may be more likely to be productive of good.

7. Use every known means throughout of securing toxin elimination, of sparing the heart from needless strain, and of tiding it over the period of greatest stress.

Résumé of Results obtained by Various Observers, and their Conclusions.—Although I have always been one who thinks that in medicine far too much regard can be given to statistics which may be inherently fallacious, yet none the less it is certain that every form of treatment will be judged by the case-mortality and incidence of complications experienced during its employment. The pathogenicity of the pneumococcus, and so the death-rate, varies greatly in different epidemics, and such factors as age and previous habits of the individual are well known to be important prognostic points: so that, if statistics are to have any value, an adequate number of

truly comparable cases treated upon orthodox lines are essential to serve as controls. This, unfortunately, is not always possible, and where it cannot be done the assumption must be made that the death-rate would have otherwise approximated to the normal, which may be taken as between 16 and 20 per cent.

Wolf¹ treated 14 cases with vaccines during an epidemic in which the total mortality was 40 per cent.: 11 of the 14 cases, or 78·5 per cent., recovered; 3 of the 14 cases, or 21·5 per cent., died.

In 10 of the 11 cases which recovered the crisis occurred within thirty-six hours of the first inoculation.

Leary² records his results in 83 cases. Of these, 34 were alcoholics, in whom the normal death-rate was 50 per cent. Of these 34 cases only 6 died—a mortality of 17·7 per cent. Of the other 49 cases only 2 died—a mortality of only 4 per cent. The death-rate among the whole 83 = 9·7 per cent.

Rapid relief of toxæmic conditions was noted, and in cases of otherwise uncontrollable delirium the abatement thereof was prompt.

Craig³ records his results in 20 cases among old sailors, all over 60, most much older (eighty to ninety years old). Most were alcoholics, nearly all had chronic nephritis, arterio-sclerosis, and dilated hearts. The average death-rate in the institution for the preceding five years from pneumonia had been 66 per cent. Yet of these 20 only 4 died, a death-rate of 20 per cent.; and of these 4 only 1 died directly from the pneumonia, this being a very severe case of bilateral disease. Of the other 3 cases

¹ *Journal of Infectious Diseases*, 1906, p. 739.

² *Boston Medical and Surgical Journal*, 1909, p. 714.

³ *Medical Record*, November 18, 1911.

one was already complicated by purulent pericarditis, and another by acute uræmia and acute dilatation of the heart.

Charteris¹ obtained much less favourable results in 19 cases. Ten simultaneous cases which seemed on the point of crisis were used as controls. His conclusions were that the administration of a stock pneumococcal vaccine had no marked effect upon the subsequent course of the disease, the mortality being practically identical—20 per cent. in the two series—that the early administration of vaccine did not abort the disease nor prevent complications, and that complications were relatively frequent in the vaccine series—viz., 1 case of meningitis, 2 of empyema, and 1 of hyperpyrexia.

It is very easy to be critical, and perhaps do injustice to other people, but a study of the paper leads to the following criticisms :

1. That the use of cases obviously about to crisis as controls is quite inadmissible.

2. That of the 4 cases which died 2 were alcoholics who were delirious or semi-conscious when treated.

3. That in only 8 of the 19 cases was a dosage of 10,000,000 of a stock vaccine exceeded. In 8 of the cases it was under 5,000,000.

4. That in 2 of those that died an initial dosage of 20,000,000 and 18,000,000 respectively was reduced subsequently to 10,000,000 and 2,000,000 respectively, although all the indications, as can be gathered from the clinical histories, were for maintaining or even increasing the dosage.

For these reasons I regard his conclusions as fallacious. His controls are inadmissible, and all that the paper

¹ *Glasgow Medical Journal*, January, 1912, p. 19.

shows is that the administration of a stock vaccine in doses already well known to be inadequate failed to reduce the mortality below 20 per cent.

Parry Morgan¹ treated 43 cases, with 2 deaths—a mortality of 5 per cent. One of these two died from nephritis after the pneumonia had subsided. Treatment was begun at periods of the disease from the second day onward, some cases being treated with stock vaccine, some with autogenous. One of these latter cases proved to be a streptococcal infection. In many cases he repeated doses of 50,000,000 of autogenous vaccine, and never saw any harm result; but he inclines to the view that a dosage of 15,000,000 to 30,000,000 gives the best result in the average adult. When an artificial crisis was not produced, the temperature often fell by lysis, with marked improvement in the symptoms. For seven of the most interesting cases as being complicated ones, and the most convincing, the original account should be consulted.

From the experience gained in the treatment of these cases, Morgan says that the temperature may be a guide, but often is not, one of the most noticeable features being the improvement in the general condition without much change in the temperature. The anxiety which one often feels for a patient is relieved, sleep comes readily, the appetite improves, and even if the pulse-rate does not fall, its strength is well maintained. At other times there is a fall in the temperature soon after the dose, sometimes even in a couple of hours. If this is the case another dose is indicated when the temperature rises again.

¹ Proceedings of the Royal Society of Medicine, vol. iii., No. 9, Supplement, p. 65.

If there is no change in twenty-four hours the dose should be repeated, sometimes being increased, but more often decreased. Between subsequent doses a longer interval may be left. For various reasons he finds the opsonic index is frequently quite unreliable as a guide to the progress of immunity in pneumonia, and feels that some other measure of it is much to be desired.

Butler Harris¹ considers that—

1. Successful inoculation for pneumonia is possible.
2. Inoculation does no harm.
3. A vaccine from one or a number of virulent strains should be used.
4. It should be introduced as early as possible.
5. The estimation of the opsonic index is not necessary.
6. The observation of the temperature and physical signs is a sufficient guide to the repetition of the dose.
7. Infections of the lung by the pneumococcus which fail to resolve after an acute pneumonia, as well as pneumococcal infections of other areas, ought certainly to be treated with a vaccine.

He found that a dose of 20,000,000 to 50,000,000 might be given without harm, that usually a fall of temperature was produced in a few hours, that frequently it rose again, but not to the same level, and that it was often necessary to repeat the inoculation once or twice. He is convinced that usually a distinct reaction in favour of the patient is produced, and that it is wise to begin inoculations before the nervous mechanism suffers much inhibition. In the sequelæ of pneumonia he considers the use of a pneumococcal vaccine as sure of a good result as that of a staphylococcal one in case of boils.

¹ *British Medical Journal*. June, 1909, p. 1530, and Proceedings of the Royal Society of Medicine, vol. iii., No. 9, Supplement, p. 103.

After comparison of the clinical histories of his cases with those of Craig and of Parry Morgan, he finds that the effects seen by each of them, as produced by bacterial inoculations in cases of pneumonia, are practically identical, and considers that every case of pneumonia should be from the outset regarded as possibly a fatal one, and suggests that a stock vaccine of proved immunizing power should always be employed as early as possible in a dose not exceeding 20,000,000, and that the preparation of the autogenous vaccine should be at once proceeded with.

This collective evidence is surely sufficient to warrant the unprejudiced in giving a fair trial to vaccine treatment of cases of pneumonia. What he is entitled to expect, and what he is not entitled to expect, therefrom has been fairly laid before him. It only remains for him to pay due heed to the various considerations, to utilize common sense and clinical experience, and to be prepared to judge results with impartiality.

UNRESOLVED PNEUMONIA.

As we have seen, the leucocytes are held to be the chief agent in the production of resolution by means of ferment which they liberate. Hence the rational procedure in a case of unresolved pneumonia would seem to consist in the promotion of a leucocytosis, and the determination of a leucocyte flow to the infected area by fomentations, blisters, and other means. Whether it has been actually observed that cases of acute pneumonia showing a relatively defective leucocytosis are especially apt to resolve badly, and that there is a leucopænia, relative or absolute, present after failure

to resolve, I know not. Observations upon these points might perchance repay the clinician for his trouble. Furthermore, as we have already seen, it is hardly reasonable to expect that the administration of a vaccine will have much immediate effect during the stage of consolidation in an acute attack. For these two reasons it would seem hardly reasonable to expect that a vaccine should have much immediate effect upon an unresolved condition. The blood and lymph stasis is, however, not then so complete as at the height of consolidation. Some attempt has been made at the re-establishment of the circulation. It therefore follows that some good may be expected to accrue from a course of vaccine treatment. It must, however, be remembered—

1. That even if the infection were an unmixed one at the inception of the attack, it is hardly likely to have remained so. The streptococcus or *M. catarrhalis* will almost certainly complicate the picture, and to these attention may have to be directed. In the few cases which I have myself investigated a mixed infection has been always present, and I have thought it the better practice to employ a mixed vaccine.

2. That progress necessarily must be somewhat slow.

3. That the production of local reactions in the infected tissues is essential to cure, and that such dosages must be used as will produce this effect. A 50,000,000 dose of any of the above three organisms will do to begin with, but should stethoscopic observations and clinical symptoms show failure of local reaction, this dosage should be increased. Personally I have found ultimate doses of 500,000,000 essential to complete cure.

Periodic examinations of the sputum should be made to check progress and eliminate the possibility of a new

infection having been incurred, and to insure the continuance of treatment until the pneumococcus has entirely disappeared from the sputum.

In one very interesting case of mine it took four months' treatment to bring about a satisfactory clinical condition, and an additional eight months to secure the desired bacteriological result.

Warren Crowe has described a very interesting case of unresolved pneumonia, where the infective agent was the bacillus of Friedländer. Within forty-eight hours of an inoculation of 50,000,000, the whole condition cleared up, although the patient had been in bed for a fortnight with high temperature and extreme dyspnœa. Three days later 100,000,000 were given, and complete recovery was very soon established.

BRONCHO-PNEUMONIA IN CHILDREN.

This condition will, I venture to predict, prove one of the most profitable of all fields for the worker in vaccine therapeutics. Ignorance of what constitutes the defensive mechanism in young children against bacterial invasion has led to a somewhat natural reluctance to apply methods applicable to the adult. The results achieved in the treatment of whooping-cough, gonorrhœal vulvo-vaginitis and conjunctivitis, show clearly, however, that children, and even infants, do respond readily to therapeutic inoculation.

In broncho-pneumonia we have a disease of such high mortality that ample justification exists for endeavours to find some specific form of treatment. The consolidated areas are not, as a rule, so large that any considerable stasis of the circulation results, as in the case

of lobar pneumonia, and from this fact additional hope of success may be taken.

Peculiar difficulties, however, present themselves. The bacteriology is a much more variable one than in the case of lobar pneumonia. Pneumococcus, streptococcus, *B. influenzae*, bacillus of Friedländer, and perhaps the staphylococcus and other organisms, may be responsible for the condition, either singly or in any combination. If vaccine treatment is to be resorted to, it is obvious that the precise nature of the infection should be determined. Unfortunately, children are very apt to swallow sputum, and it may be impossible to get specimens for examination. If they can be got, then all, so far, is well; if they cannot, lung puncture is also liable to prove a failure owing to the small size of the consolidated areas. Blood-cultures might prove of service, but so far as I know no observations have been made in this direction. If specimens of sputum can be obtained, the best procedure would appear to be to make examination at once of stained smears, and administer stock vaccine of proved immunizing power corresponding to the infection found, while the autogenous vaccine is in course of preparation. If no specimens are obtainable, and lung puncture and blood-culture fail, then I think it will be more than justifiable to employ a stock vaccine of the following composition: Pneumococcus, 10,000,000; streptococcus, 10,000,000; *B. influenzae*, 20,000,000; bacillus of Friedländer, 20,000,000 in each c.c. The dosage to be, under three years, 2 minims; three to five years, 4 minims; five to seven years, 6 minims; over seven years, 8 minims, the indications for repeating or increasing the initial dosage being general condition in the first place and temperature in the second. As a general rule, young

children bear relatively high dosages of vaccine extremely well.

Of published results achieved in broncho-pneumonia there are none as yet available, but one or two private communications which I have received are very favourable to this therapy.

EMPYEMA, LUNG ABSCESS, AND BRONCHIECTASIS.

There is nothing specially to mention as regards the vaccine treatment of these conditions. Treatment will be guided by the considerations which govern the procedure in all cases of abscess formation and of sinuses in the body generally.

Prevention, as always, is better than cure, and that a considerable reduction is effected in the incidence of these and other complications by the early application of vaccine treatment to all cases of pneumonia is agreed on by all who have had mature experience of this procedure.

In the case of lung abscesses especially is the bacteriology apt to become a very complicated one as time goes on. *Streptococcus*, *M. catarrhalis*, *B. coli*, *B. proteus*, *B. pyocyaneus*, *B. influenzae*, *M. tetragenus*, and bacillus of Friedländer, are a few of the accessory microbes which may make their appearance, and in the preparation and use of the autogenous vaccines considerable discrimination and care may be required. Free drainage is a *sine qua non* to cure in such cases as these, and there might seem to be reasonable grounds for the fear that vaccine treatment might bring about closure of the vent or sinus, and induce local accumulations of pus. In practice it would appear that this danger may be easily

exaggerated. I remember one patient whom I was treating with a mixed pneumococcus, streptococcus, *B. influenza* vaccine for chronic antral trouble, who was also suffering from an old lung abscess, which sometimes discharged by bronchus as well as through a persistent external sinus, expressing great anxiety when he found that what he regarded as his safety vent was closing up. I reassured him, and treatment was continued, with the result that he has not lost a day's work for two years, and that antrum and lung abscess have caused no further trouble. None the less it is wise whenever possible to make sure that any sinus is healing from the bottom by occasional probing and the instillation of eitrated salt solution.

In three cases of bronchiectasis and lung abscess I have secured an apparently durable cure, for they have remained well for over two years. A fourth very bad case is doing exceedingly well, and is still under treatment.

Small dosages are best at the beginning of treatment, but as time goes on they should be increased with boldness. A slight constitutional reaction and alteration in the character and amount of discharge are the best indications of adequate dosage.

WHOOPING-COUGH.

Bacteriology.—That the bacillus of Bordet-Gengou is the true specific cause of whooping-cough is now generally accepted, the various serum reactions affording strong confirmatory evidence. Early in the attack the Bordet bacillus appears in great numbers in the secretions, but the careful investigations of Freeman and of Martha Woolstein into the bacteriology of this

disease have shown that even then it has very frequently associated with it the *B. influenzae*, and often the pneumococcus. The great liability to such complications as bronchitis and broneho-pneumonia is thus explained in precisely the same way as the liability of so-called 'influenza attacks' in the adult to develop into acute pneumonia.

As early even as the end of the second week the Bordet bacillus has almost disappeared from the secretions, whereas the *B. influenzae* and pneumococcus, and perhaps the streptococcus and *M. catarrhalis*, have increased considerably in numbers. A pure infection is so rare an occurrence that the symptoms referable to the Bordet bacillus alone may be almost said to be unknown. The bearing of this upon the vaccine treatment of whooping-cough will be dealt with presently.

Vaccine Treatment.—The first attempt at the establishment of immunity to the disease was made by Bordet about ten years ago. He inoculated twelve healthy children with large doses of a vaccine; very soon afterwards they came in accidental contact with a case of whooping-cough, with the result that they all immediately fell victim to very severe attacks of the disease. The explanation of this occurrence is now taken to be that contact took place during the period of lowered resistance (of 'negative phase') consequent upon the use of very large doses of the vaccine. This view presented itself to Freeman, and on p. 97 of the Proceedings of the Royal Society of Medicine, vol. iii., No. 9, Supplement, he gives a detailed account of the many careful observations which he made in order to determine the correct therapeutic dose. Doses varying from 2,000,000 to 120,000,000 were employed, the final conclusion being that a dosage

of about 100,000,000 gives the best results, and that a weekly repetition is quite safe. By these means he found that the average duration of the disease in his vaccinated cases was reduced to 4·3 weeks, as compared with 7·4 weeks in those who received inoculations of saline solution, and served as controls. It must be remembered that many of these cases were treated with dosages which Freeman now recognizes to be inadequate, and that no specific treatment was directed against the complicating organisms, such as the pneumococcus and *B. influenzae*. This he now advises shall be done as a matter of routine, and my own limited personal experience is entirely confirmatory of the correctness of this procedure. The following scheme of dosage may be safely followed :

Age.	<i>B. Bordet.</i>	<i>B. Influenzæ.</i>	Pneumococcus.
Under 1 year ..	25	10	2
1-2 years ..	50	25	5
2-3 „ ..	100	50	5
3-7 „ ..	100	50	10
Over 7 years ..	100	100	10

Reinoculation may be performed at intervals of five to seven days, and at the third inoculation a double dosage may be employed, if thought advisable.

As a prophylactic the initial dosage corresponding to the age may be doubled in seven days ; and this again doubled if thought advisable after another seven days.

The employment of the above combined vaccine for this purpose may also be expected to diminish the liability to broncho-pneumonia, and is devoid of all risk.

As to the duration of the immunity thereby conferred

we as yet know nothing ; probably it is about six months, so that two series of inoculations yearly may suffice to confer the desired protection.

Saunders and collaborators have described (*Pediatrics*, March, 1912) their results in forty cases of whooping-cough, and in fourteen children who had been exposed to contagion. They also began with small doses—viz., 5,000,000—but soon concluded that the dose was too small, and increased it to 10,000,000 or 20,000,000, repeated as required. Despite the fact that this increased dosage is still an inadequate one, they obtained results which led them to the following conclusions :

1. That as a prophylactic the vaccine has a decided value ; that whilst it is true that vaccination or some other infection will postpone or interrupt the course of pertussis, vaccine alone will absolutely prevent it. The immunity is of uncertain duration, but the injections may be repeated, and it is of the utmost importance to postpone the disease until the child has passed the age of two. The failures reported by some observers must be attributed to an impotent vaccine or to insufficient dosage.

2. That as a remedial agent success depends upon the promptness of administration and the freedom from complications at the time.

3. In no case should other treatment be withheld if indicated, especially in infants, who may be spared convulsions or broncho-pneumonia by the use of emetics, sedatives, or some aromatic compound.

4. It is quite possible that much better results may be obtained in late cases by the use of larger doses (and the combination of vaccine directed against the allied organisms).

5. That in view of the high mortality from pertussis in

young children there should be a systematic effort made to determine the duration of artificial immunity and to keep them protected.

ACTINOMYCOSIS OF LUNG (see p. 171).

PHTHISIS.

As it is quite impossible in this small book to devote to the study of the vaccine treatment of phthisis space commensurate with the importance of the subject, I have decided to consider a few only of the more important points somewhat fully, and for a fuller discussion must refer the reader to 'Bacterial Diseases of Respiration.' The points which I shall deal with here are the following : (A) Mixed infections : (1) their nature ; (2) import ; (3) prevention ; (4) treatment—method of controlling dosages and intervals—results ; (5) limitations to the applicability of vaccine treatment. (B) Infection by the tubercle bacillus : (1) its nature and diagnosis ; (2) constitution of the tubercle bacillus and of the tuberculins : (3) immunity against the bacillus—the tuberculin reaction ; (4) choice of tuberculin—methods of controlling dosages and intervals ; (5) autoinoculation.

A. MIXED INFECTION.

Attention is first directed to the subject of mixed infection, because only rarely is phthisis, as seen by the average medical man, a pure invasion by the tubercle bacillus. It is very probable that mixed infection is present in all instances where tubercle bacilli are present in the sputum. and, indeed, in many instances it is highly likely that invasion by other bacteria preceded the access of the tubercle bacillus to the pulmonary tissues, and paved

the way before the latter. As we shall see later, practically every symptom which is commonly ascribed to the activities of the specific organism may be likewise due to the energies of the so-called secondary, but which very often are truly the primary invaders. Logically, the treatment of all cases of pulmonary tuberculosis, where tubercle bacilli and other pathogenic organisms are associated together, should primarily concern itself with the extinction of the latter, for the tendency of lesions produced by the former is, in the great majority of instances, to natural cure.

1. *The Bacteriology of Mixed Infections.*

The determination of its precise nature in any given case requires considerable care, as fallacies are very apt to be introduced either from insufficient care in the collection of the specimen, dirty receptacles being employed, or adequate precautions not being taken for the exclusion of contaminations due to post-nasal catarrh, pyorrhœa alveolaris, or follicular tonsillitis, or from failure to make careful direct examinations of the specimen, and to employ culture media suited to the growth of all such varieties of bacteria as may be present. I have made very careful examination by direct and cultural methods in fifty-two cases, and found as follows :

Streptococcus	in 42 cases = 81 per cent.		
<i>M. catarrhalis</i>	„ 41	„ = 80	„
Pneumococcus	„ 19	„ = 37	„
<i>B. influenzae</i>	„ 12	„ = 23	„
<i>M. paratetrageus</i>	„ 10	„ = 20	„
<i>Staphylococcus albus</i>	„ 8	„ = 15	„
<i>Staphylococcus aureus</i>	„ 6	„ = 12	„
Diphtheroid bacillus	„ 3	„ = 6	„
Bacillus of Friedländer	„ 2	„ = 4	„
<i>B. proteus</i>	„ 2	„ = 4	„
<i>B. coli</i>	„ 1	„ = 2	„

These results agree closely with those of Hastings (quoted in Klebs's 'Tuberculosis'). Other observers find the staphylococcus of almost universal occurrence, but this I believe to be due—(1) to insufficient care in exclusion of contaminations; (2) to the conduct of their observations upon very advanced cases. For I am convinced from my own observations that in early cases the catarrhal organisms are of much more frequent occurrence than are the more purely pyogenic organisms, such as staphylococcus, *B. coli*, and *Streptococcus longus*. In the early cases the variety of streptococcus present is usually the 'salivarius' or 'mucosus.'

The conditions under which the patient lives also have considerable influence upon the nature of the mixed infection. In those who live in pure mountain air the secondary infection is usually due to a short streptococcus, *M. catarrhalis*, or pneumococcus; the organisms are few in numbers, monorganismal infections are common, and binorganismal the rule. In advanced cases, and in those that live in unfavourable surroundings, multiple infections are almost the invariable rule, and it is common to find associated together catarrhal and pyogenic organisms.

2. *The Import of Mixed Infections.*

The allied invaders in cases of pulmonary tuberculosis may play a complex rôle: they may exert an influence similar to that which they exert in other parts of the body and peculiar to themselves—viz., they may cause pus formation, and so induce consolidation and cavitation; they may produce catarrhal symptoms, and so increase the apparent area of lung involved, and cause increased expectoration; they may elaborate toxins

which may enter the general circulation, and lead to all the resultant symptoms of toxæmia, rapid pulse, high temperature, malaise, anæmia, and loss of weight ; finally they may exert a direct influence upon the rate of multiplication of the tubercle bacilli. The truth of these statements will be evidenced when we come to consider the results of treatment directed against these allied invaders ; at present I shall merely enlarge upon the last of these points. It is well recognized that some bacteria or their toxins have a marked inhibitory action upon the rate of multiplication of other bacteria ; for instance, if the bacillus of Friedländer and almost any other bacterium be incubated together in a suitable culture medium, the former organism will grow to the complete exclusion of the latter. On the other hand, the rate of growth of certain bacteria is greatly accelerated by the presence of other bacteria or their toxins ; for instance, the *B. influenzae* grows much more rapidly when the pneumococcus, streptococcus, staphylococcus, or *M. catarrhalis*, is allowed to grow in symbiosis with it. Finally, the growth of a certain organism may be entirely uninfluenced by the presence of another variety ; thus the staphylococcus and streptococcus apparently exercise no influence on the rates of multiplication of each other. Now, in a very large series (several hundreds) of experiments which I have conducted,¹ I have found that the concomitant invaders in cases of pulmonary tuberculosis may exercise a very pregnant influence upon the associated tubercle bacillus. In most instances they cause a very great acceleration of the rate of growth in artificial culture of the latter organism ; in some cases,

¹ For method see *Journal of Vaccine Therapy*, November, 1912, or 'Bacterial Diseases of Respiration.'

however, they appear to produce no such effect, and in these instances the defect lies not with the allied invaders, but with the *B. tuberculosis*, whose growth seems to be incapable of stimulation, not only by the toxins of the associated organisms, but also by those of organisms derived from other cases of phthisis. These facts are of considerable practical importance, for clinical experience has shown me that in the former instance the patient will gain much from treatment with vaccines of the allied invaders, whereas in the latter instance he will apparently gain little or nothing. In all cases of phthisis of which I now have charge I make it an invariable rule to test the influence of the toxins, derived from the organisms present in mixed infections, upon the rate of growth of the associated *B. tuberculosis*, as the rapid isolation of the latter by means of the antiformin method is now a simple matter ; in this way I am enabled to determine with little delay the cause of any apparent failure on the part of autogenous vaccines of the allied invaders to influence favourably the progress of a case.

3. *The Prevention of Mixed Infections.*

As mixed infections may be of such serious import to the patient, it obviously behoves us to prevent their access if they have not already gained a footing, or to limit the variety of the constituents if one or more allied invaders be already present. We have already seen that the commonest invaders are the streptococci of the mouth and the catarrhal organisms ; it therefore follows—(1) that in cases of pulmonary tuberculosis especially should the strictest attention be paid to the hygiene of the mouth and nose—a condition of pyorrhœa alveolaris, follicular tonsillitis, or post-nasal catarrh should be

promptly and adequately treated, and carious teeth, adenoids, and nasal obstructions should be removed ; (2) that periodic immunization against the more important catarrhal organisms, especially the *M. catarrhalis*, pneumococcus, and *B. influenzae*, is likely to diminish greatly the danger of incurring any superadded infection, and so of diminishing the area of lung available for the aeration of the blood, and of added strain being thrown upon the musculature of the heart. This is best done by the use of my combined vaccine for colds, in the manner described on pp. 336-339.

4. *The Treatment of Mixed Infections.*

We are here concerned intimately only with the method of treatment by means of vaccines, but it must be remembered that this forms only part of the treatment available to our use. An ample supply of pure air, best from the moors or mountains, will do much to limit mixed infection, while continuous inhalations of suitable antiseptic vapours, such as those derived from either of the following solutions, have been found of great service :

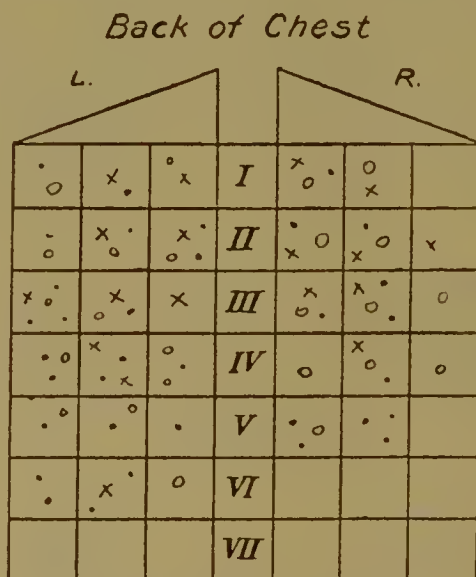
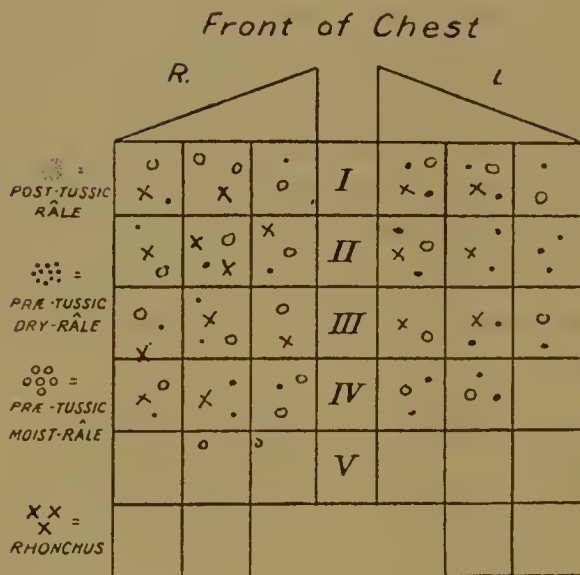
R Tinct. iodi ..	..	} <i>āā partes æquales.</i>
A. carbol. liq. ..	..	
Creosoti ..	..	
Etheris ..	..	
Sp. rect. ..	..	
Fiat mistura.		

OR—

R Menthol ..	..	..	̄ii.
Creosoti ..	..	..	̄i.ss.
Sp. camphoræ ..	..	..	̄i.ss.
Sp. rect. ..	..	..	ad ̄i.
M. et f. m.			

Sig.: Twenty drops of either of these mixtures to be used every hour to moisten the wool inside the respirator.

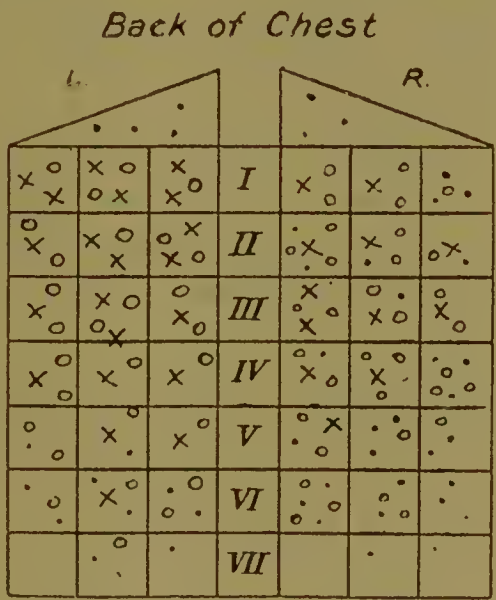
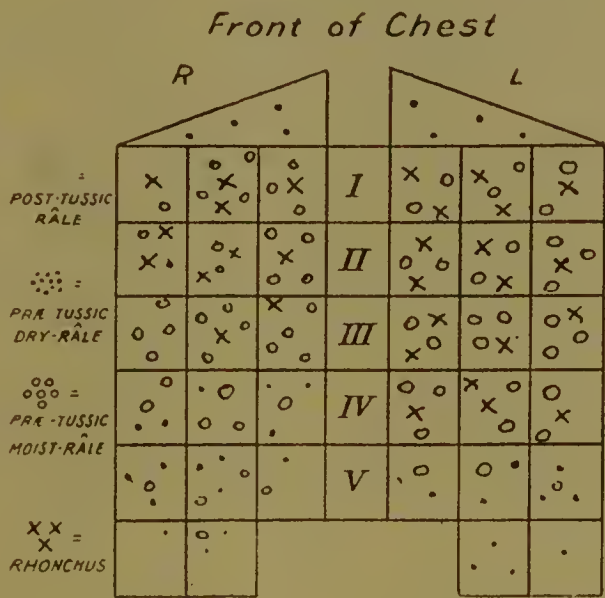
VACCINE THERAPY

CHART XII^a.

BEFORE FIRST INOCULATION.

Sputum = 6 ozs. per day.

CHART XII^b.



TWELVE HOURS AFTER FIRST INOCULATION.
Sputum = 10 ozs. per day.

Other observers claim to derive beneficial results from the use of intratracheal injections of menthol, guaiacol, or iodoform, dissolved or suspended in olive oil, and yet others from the intravenous use of weak solutions of formaldehyde or iodoform. The measure of success achieved, however, has not been such as to cause any of these methods to be regarded as a specific cure ; that of continuous inhalation apparently is productive of the most benefit, but some difficulty may be experienced in inducing the patient to be sufficiently persistent.

Vaccines certainly offer the best chance of bringing about the desired result, but if this is to be secured, great care must be taken in seeing that the vaccine is the appropriate one, and that it is administered to the best advantage.

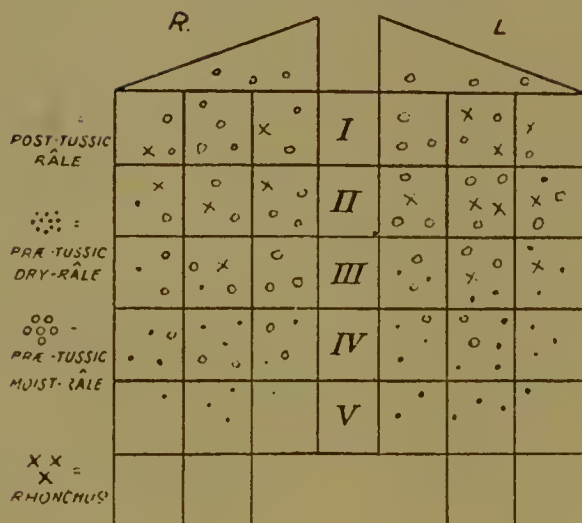
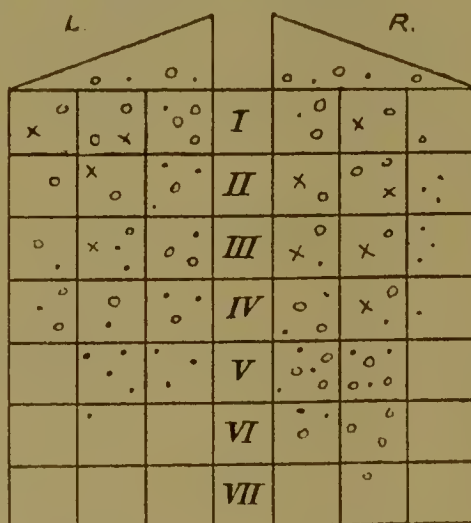
It will be quite apparent from what has been already said that an autogenous vaccine, carefully prepared from carefully taken and selected specimens of sputum, will have great advantages over any stock or heterologous vaccine. If financial or other reasons compel the use of these latter, one prepared by the addition of some mixed staphylococcus vaccine to my combined vaccine for colds will probably prove as serviceable as any.

Method of Controlling Dosages and Intervals.—Let us assume that autogenous vaccines of the allied invaders are available, and that we are in a position to administer initial dosages such as the following : Pneumococcus, streptococcus, *B. coli*, 25,000,000 ; *M. catarrhalis*, *M. paratetragenus*, bacillus of Friedländer, *B. proteus*, 50,000,000 ; *B. influenzae*, diphtheroid bacilli, staphylococcus, 100,000,000. Our procedure will then be as follows :

The patient is kept in bed in a warm, but well-ventilated, room, observations are taken every four hours of the temperature and pulse-rate, the daily amount of sputum measured, and careful stethoscopic examination of the chest made daily, and recorded on suitable charts. When the patient has settled down into a more or less constant condition as regards pulse, temperature, expectoration, and physical signs (see, for instance, Chart XII^a), an inoculation of the appropriate initial dose of the selected autogenous vaccine is given at between 8 and 10 p.m., such an hour being selected for the reason that definite signs of the production of local reaction within the lungs should be in evidence after about twelve hours, and may be watched throughout the following day. Careful observations of the patient are therefore made after intervals of twelve, twenty-four, and forty-eight hours, and daily thereafter. If the vaccine be compounded of organisms intimately concerned in the production of the signs and symptoms, and an adequate dosage have been administered, a definite effect should be produced in any one or more of the following directions by the end of twelve hours :

1. There may be a rise in pulse-rate of 10 to 20 beats.
2. There may be a rise in temperature of 0.5° to 1.5° F.
3. There may be an increase in the quantity of sputum.
4. There may be an increase or alteration in the physical signs, and of these the last is the most important, for it is only by the production of local reactions of moderate degree that immunizing responses can be brought about to the best advantage (Chart XII^b).

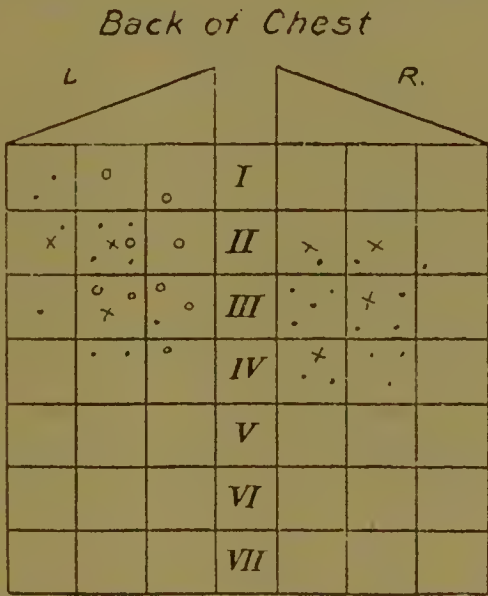
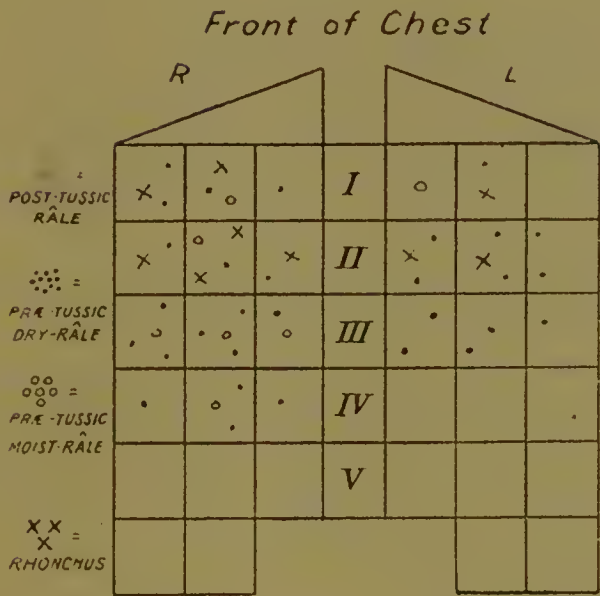
Fresh examination at the end of twenty-four hours should show a swing-back in the condition of the patient in one or more of the following directions :

CHART XII^c.*Front of Chest**Back of Chest*

TWENTY-FOUR HOURS AFTER FIRST INOCULATION.

Sputum = 6 ozs. per day.

CHART XII^d.



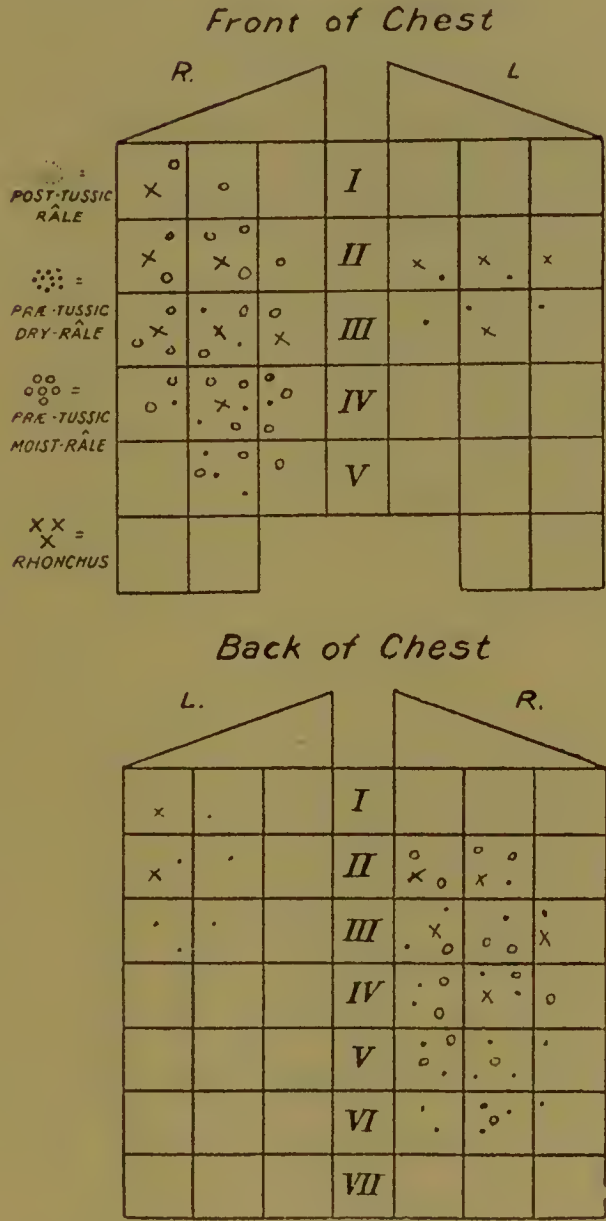
SEVENTY-TWO HOURS AFTER FIRST INOCULATION.
Sputum = 2 ozs. per day.

1. The pulse-rate should have fallen to its old level.
2. The temperature should have fallen to its old level, or to a lower one.
3. The sputum should be diminishing in quantity.
4. The physical signs should be improving, and may correspond to what they were before the inoculation, or a certain amelioration may have been already produced (Chart XII^c).

After forty-eight hours the changes noted after twenty-four hours should have advanced farther in the same direction (Chart XII^d). In some instances there is a delayed reaction; the changes which have been described as typical after twelve hours may not be evidenced till the twenty-fourth hour, and those of the twenty-fourth hour not till the forty-eighth hour.

At the end of seventy-two hours there may be a further improvement in the clinical signs of the patient, and this may continue for several days (Chart XII^e). A time will, however, come—largely dependent on the dose of vaccine given—when, in place of improvement, a retrogression will be initiated; this is the signal for reinoculation. It is wise to repeat the initial dosage once, even if the reaction obtained was very slight, but thereafter increase of dosage is indicated by failure on the part of the patient to continue or maintain improvement for at least four days. Occasionally it will happen that no reaction whatever is obtained; this indicates one of two things—either (*a*) that the dose was too small, or (*b*) that the vaccine itself was inappropriate. If the former alternative be thought likely, a double dosage should be given at the expiration of seventy-two hours, and observations conducted as before; this should always be done before assuming the latter alternative, that the vaccine is inappropriate,

CHART XII^c.



SIX DAYS AFTER FIRST INOCULATION. SECOND INOCULATION.
Sputum = 3 ozs. per day.

CHART XIII.

Front of Chest

	R.				L.		
	x	o o	o	I		o	o
POST-TUSSIC RÂLE	o	x o	o			o	o
	o	x o	x o	II	x o	x o	x
	x	x o	o				
PRE-TUSSIC DRY-RÂLE	o	o x	o	III	o o	x o	x
	o	o	o		o	o	o
	o	o	o	IV	o	o	o
PRE-TUSSIC MOIST-RÂLE	o	x o	o				
	o	o o	o	V			
	o	o	o				
XX = X = RHONCHUS							

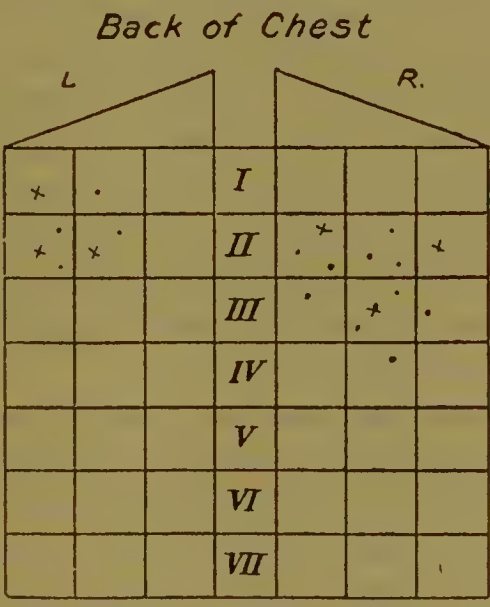
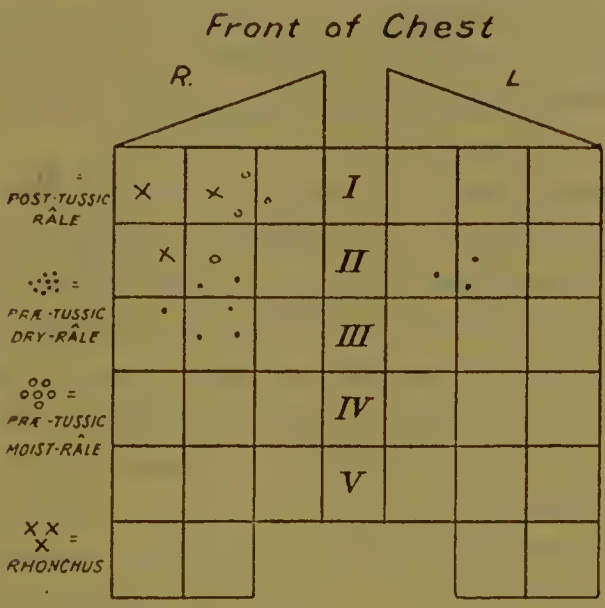
Back of Chest

	L.				R.		
	x	o	o	I	o	o	
	x	o	o				
	x	x	x	II	o x	x o	o
	o	o	o		o	o	o
	x	o	x	III	o o	o o	o
		o			o	o	o
				IV	o o	x o	o
					o	o	o
				V	o o	o o	o
					o	o	o
				VI	o o	o o	o
					o	o	o
				VII	o	o	o

.. TWELVE HOURS AFTER SECOND INOCULATION

Sputum = 4 ozs. per day.

CHART XIIg.



FORTY-EIGHT HOURS AFTER SECOND INOCULATION.
Sputum = $\frac{1}{2}$ oz. per day.

being compounded either of organisms not concerned at all in the production of the pathological changes, or else of such bacteria as we have seen live in symbiosis with the tubercle bacillus, without producing any stimulation upon the rate of growth of the latter organism.

If these procedures be carefully carried out, it will be found that in those cases in which the secondary infection is a multiple one there is a marked difference in the response which is made to inoculation with the several vaccines, some producing more effect upon the patient generally, and the physical signs in particular, than do others. The interesting fact now appears that in the majority of cases that vaccine produces the greatest effect which likewise *in vitro* produces the greatest acceleration upon the rate of growth of the tubercle bacillus, and that this organism is not necessarily the one which predominates either in smears or in cultures. Personally, I now always check the results of clinical observations after administration of a given vaccine with the experimental results obtained *in vitro*, proceeding, however, to obtain the former without waiting for the development of the latter, which serve chiefly to throw light upon any obscure results, or failure to secure improvement from the use of the autogenous vaccines.

While it must be admitted that these systematic observations require the expenditure of considerable time and care, I have never yet failed to be more than recompensed. The responsive powers of the individual, the appropriateness of the vaccine itself, of the dosages and intervals, are ascertained with almost mathematical exactitude, and when the series of observations have been minutely performed over the first three or four

inoculations, it becomes possible almost to predict the physical condition which will obtain in the chest on any given day, and the procedure becomes much simplified, stethoscopic observations being necessary, as a rule, only at the following intervals: twelve hours, three days, and five days. If retrogression is apparent on the fifth day, reinoculation is then performed, otherwise it is delayed until the seventh or eighth day.

Results of Vaccine Treatment.—Inasmuch as I believe that the only really scientific way of employing vaccines in pulmonary tuberculosis is according to the above methods, and these have so far been so little used, it is obviously impossible to give any expression of opinion as to what vaccines are really capable of effecting. Reference to the series of charts in ‘Bacterial Diseases of Respiration,’ as well as to the one series here included, will show what great changes can be produced in the physical signs by the use of vaccines directed against the allied invaders, and justify my contention that it is quite impossible from the examination of any tuberculous chest to estimate the area of lung actually involved by the tuberculous process; for whereas in certain cases we learn subsequently, from the use of tuberculin in a precisely similar way to that in which we used the vaccine, that the area of lung involved in the tuberculous process corresponds fairly well with the area over which physical signs are to be detected in the first instance, in other cases we learn that the area involved by the tubercle bacillus corresponds more or less closely to the area over which physical signs are to be detected only after the application of a full course of vaccine treatment directed against the allied invaders. It therefore follows that the only proper time to apply tuberculin therapy to a case

of pulmonary tuberculosis to which mixed infection has gained access is when a course of methodical treatment with the vaccines of the allied invaders ceases to produce further improvement in the clinical condition of the patient.

What may be reasonably expected in most cases from the use of autogenous vaccines is as follows :

1. Considerable diminution in the physical signs.
2. Reduction in the temperature and pulse-rate.
3. Reduction in the amount of sputum.
4. Improvement in the general condition of the patient.

Occasionally the physical signs may be caused to disappear almost in their entirety, although tubercle bacilli are still being expectorated in scanty numbers ; occasionally a reduction may be brought about in a pyrexia, which even the most absolute rest has failed to influence materially ; sometimes a patient who is placed under favourable circumstances, and is treated with a vaccine of the allied organisms, makes an unexpectedly rapid and complete recovery, while frequently a vaccine will at once turn the scale, especially in subacute and chronic cases which have failed to improve beyond a certain point, and threaten to retrogress.

Webb¹ summarizes as follows the results he obtained in fifty cases of pulmonary phthisis in which vaccine treatment was directed against the allied invaders.

- ‘ 1. In no case has a patient been harmed.
- ‘ 2. Many patients have had exacerbations more rarely.
- ‘ 3. Expectoration in nearly all cases has been lessened ; nocturnal coughs have frequently been eliminated ; evacuations of 4 to 6 ounces of sputum daily have in several cases been reduced to less than 1 ounce.

¹ Klebs's ‘Tuberculosis,’ p. 598.

‘ 4. Concomitant pus affections have cleared away, such as suppuration of ears, staphylococcic acne, and sycosis.

‘ 5. When these vaccines have been combined with small doses of Koch’s New Tuberculin, spreading infiltrations have been averted and cleared up.

‘ The impression has been gained that the bronchorrhœa type of cases has, perhaps, received less benefit connected with the reduction of sputum than the cavernous type.’

Pottenger¹ says : ‘ In the treatment of advanced cases of pulmonary tuberculosis we are often able—*i.e.*, by general methods—to arrive at a result which is very satisfactory compared with the condition at the beginning of treatment. We can often secure a healing of all but a small focus, which keeps on secreting month after month. In such cases it seems probable that if we could but combine with tuberculin the appropriate vaccine made from the culture of the associated microbes we might heal these lesions completely. I do not doubt that the true remedy for mixed infection will be obtained in a vaccine made from the cultures taken from the strain of the micro-organism found in each individual patient. The results which we have so far obtained in our endeavours to treat in this manner are very encouraging.’

Bonney² gives a very good account of the results he obtained in twenty-eight cases as follows :

‘ In Group 5 are embraced patients exhibiting the persisting fever of mixed infection who were subjected to injections of homologous vaccines without tuberculin therapy. There are twenty-eight patients in this class displaying active tuberculous processes, with profound

¹ ‘ Pulmonary Tuberculosis,’ 1908, pp. 257 and 261.

² *Ibid.*, 1910, pp. 911-918.

constitutional disturbance. The vaccines were not administered to any patient in this group until the futility of hygienic measures without specific medication had been demonstrated beyond question. In view of the fact that the mixed infection is often the determining factor in turning the scales irretrievably against recovery, it was deemed justifiable to resort to the use of bacterial vaccines for patients apparently doomed to a fatal termination. An early control of the septicæmia offered the only natural basis for hope regarding nearly all invalids included in this group. . . . All individual vaccines were prepared from cultures grown from the secretions of the patient. In nearly all cases the disease had been of long standing, the duration having been less than one year in but three instances. While a few patients had been under observation from time to time during a period of several years, the acute septic manifestations had been of comparatively brief duration. It is important to note that the twenty-eight cases are divided into two general subdivisions, the first twenty-two comprising one class, the last six another. Among the patients in the former class the physical condition was extremely urgent in all cases, the prognosis very unfavourable in five, doubtful in two, and utterly hopeless in fifteen. In these cases the vaccine medication was employed in a last effort to reduce temperature, and possibly aid thereby in saving or prolonging life.

In the second sub-group very satisfactory improvement had been secured in each instance. The nutrition was excellent, with complete absence of fever, almost entire arrest of the activity of the tuberculous process, and a uniformly good prognosis ; in these cases, however, the cough and expectoration represented important

disturbing features. In noting the results of vaccine therapy it is necessary to discriminate between the apparently hopeless cases of one class, and those without temperature elevation, or other grave features, in the second group. Of the twenty-two cases in the former, all of whom, by virtue of every consideration ordinarily influencing prognosis, were destined to an early fatal termination, eight are recorded as having achieved improvement to such an extent as to justify an unqualifiedly favourable prognosis, with almost complete arrest of the tuberculous process. Thus in more than one-third of the cases the entire clinical picture was unexpectedly transformed, following vaccine medication. In six patients there was observed at first a material improvement, but this was followed by a subsequent retrogression, death taking place in each instance, although in one case as a result of a sudden pulmonary hæmorrhage. In seven instances no appreciable results were observed following the vaccine medication, and the patients finally succumbed to the disease.

‘ In the second class, comprising six cases exhibiting a favourable prognosis, the vaccine was administered solely in the hope of controlling distressing cough and lessening expectoration. In one case the results were highly gratifying, but in the remaining five not the slightest influence could be properly attributed to the vaccine. These results suggest a much more limited field of usefulness for the homologous vaccines in afebrile cases than in those with acute septic manifestations. While generalizing statements in connection with clinical observations of this character are hardly appropriate, the evidence appears conclusive that some benefit may be expected to attend the employment of such an agent in a fair

proportion of cases otherwise adjudged incapable of improvement.'

Reference to Bonney's table is necessary in order to appreciate the striking nature of the results achieved in some of the cases.

5. *Limitations to the Applicability of Vaccine Treatment.*

While I cannot at all agree with Bonney's deductions from his results in five cases that there is a more limited field of usefulness for the homologous vaccines in afebrile cases than in those with acute septic manifestations, I do agree with him that very striking results are sometimes seen in pyrexial cases. Pyrexia is no contra-indication to vaccine treatment unless it is associated with the rapid pulse of a heart which is beginning to fail; in such cases I have never seen the slightest benefit accrue from vaccine treatment. Tuberculosis of the broncho-pneumonic and miliary types seems to be quite unresponsive to this therapy, which I have also found to fail in two chronic cases with little temperature, where the mixed infection was due to *Staphylococcus albus*, and cultures of this organism, when properly tested, failed entirely to influence the rate of growth *in vitro* of the associated tubercle bacillus. It was not that these two cases did badly, but the marked improvement that was produced was referable to general hygienic methods and tuberculin treatment, the autogenous vaccines simply proving quite devoid of power, whether used in doses of 100,000,000 or 4,000,000,000.

B. INFECTION DUE TO THE 'BACILLUS TUBERCULOSIS.'

1. *Nature of the Infection.*

Sufficient evidence has now been accumulated to convince most minds that are open to conviction that the human and bovine strains of the tubercle bacillus are distinct, though closely related, types. Just, however, as there are intermediaries between the *B. typhosus* and *B. coli*, so there are intermediaries between the human and bovine types of the tubercle bacillus; but these are only rarely encountered. While infection by the bovine type is quite common in young children, it becomes less and less common with advancing years, and I think it must be admitted that Spengler was wrong in attributing a very considerable percentage of cases of pulmonary tuberculosis to infection by the bovine type either alone or in conjunction with the human strain. Bovine pulmonary tuberculosis in adults would appear to occur in less than 5 per cent. of all cases of phthisis. None the less there are certain definite advantages derived from employing highly polyvalent tuberculins, derived from both human and bovine strains, in the treatment of this disease, and this procedure is the best alternative to the preparation and use of the autogenous tuberculin.

Diagnosis of Tuberculosis.—In the early diagnosis of tuberculosis lies the best chance of effecting a complete cure. To facilitate this end numerous means have been devised, but it is quite impossible here to enter into a discussion on this point. Various clinical methods and observations may be employed, the help of X rays sought, and such reactions utilized as those devised by Calmette and Wolff-Eisner, von Pirquet, Moro, and Carle Woodcock.

Here I propose to describe two methods only—one a comparatively new chemical method, which I have found to be of decided help in doubtful cases, the albumin test of Roger; the other, the oldest test of all—viz., the diagnostic use of Old Tuberculin, which I agree with Bandelier and Roepke, Moeller, Freymuth, and others in regarding as perfectly safe when properly employed, and as giving by far the most reliable results of all.

Roger's Albumin Test is performed as follows: To 5 c.c. of the sputum 20 c.c. of normal salt solution and 5 or 6 drops of strong acetic acid are added. The mixture is well shaken and filtered, and the filtrate tested for albumin in any of the usual ways—i.e., by boiling, the addition of nitric acid, potassium ferrocyanide, or trichloroacetic acid. If the result is doubtful, a fresh portion of filtrate should be further diluted with 1 or 2 parts of the salt solution, and again tested. In order to secure reliable results the sputum must be fresh, and the inclusion of saliva avoided as much as possible. Roger, Buitron, Vercesi and Lesieur, and Privey have carefully observed the results given by this test, and have found—(1) that of cases without physical signs, which subsequently proved to be tuberculous, at least 75 per cent. gave a positive reaction; (2) that in all cases with tubercle bacilli in the sputum the result was positive; (3) that in miliary tuberculosis and pleurisy the result was not constant; (4) that cases of acute lobar pneumonia reacted, and that when the reaction persisted into convalescence a new focus or a complication was indicated. Acute broncho-pneumonia and acute pulmonary œdema were also positive. On the other hand, in acute bronchitis it was usually negative, in chronic bronchitis and in emphysema always so. In cardio-renal cases a positive reaction was often seen.

A positive reaction, therefore, indicates a pulmonary origin of the exudate, and excludes a bronchial source, and the more marked and constant the result the greater the likelihood of phthisis or pneumonia.

My personal experience of the test is not extensive, but this I can say, that in the few cases of doubtful pulmonary tuberculosis where physical signs were almost absent, and tubercle bacilli not present in the sputum, and a positive reaction was given to the albumin test, subsequent events confirmed the accuracy of the deduction in each instance.

The Old Tuberculin Test.—If a healthy individual receive an injection even so large as 0.01 c.c. of Old Tuberculin (Koch), no symptoms beyond slight local tenderness will be exhibited. The case is very different with a person afflicted with tuberculosis, especially if in an early stage. If the dose of tuberculin be extremely small, no effect may be noted; if larger, a local hyperæmia of the infected area; if still larger, a congestion; while if larger still, a constitutional disturbance of varying degrees of severity will result. If the infected areas be visible, as in the larynx or pharynx, the hyperæmia and congestion can be readily detected. In the lung there is an increase in the symptoms, confined to the area of infection; the auscultatory signs are magnified, and resemble a catarrhal condition of greater degree. Fine râles may appear where none were to be found previously, or their number may increase. Careful charting of the signs before and during the reaction is therefore necessary.

It is possible to have this local reaction without any general one. If the latter be present, a few hours after the administration of a small dose of tuberculin the patient begins to feel a little nervous or tired, and perhaps

has a heavy feeling about the limbs. With this there may be a slight rise of temperature of a fraction of a degree or a slightly accelerated pulse. With a larger dose the tired feeling and heaviness of the limbs becomes a true ache, which extends to the back and head, and the feeling is that of an oncoming cold. With this the temperature usually rises one or two degrees, and the patient may develop a cough where none was present before. If the dose be still larger, the patient may have a rigor, and nausea and vomiting occur.

The more experienced the physician, the less the amount of general reaction that he requires to establish a diagnosis, and an endeavour is made so to adjust the dose that a rise, at all events, of not more than 1° F. shall occur in the temperature. If this be already above 100° F., the use of the test is contra-indicated—at all events, until rest and other appropriate means have reduced the temperature to the region of the normal.

Inasmuch as the reaction usually shows itself in from eight to twenty hours, the dose of tuberculin is best given at eight or nine o'clock at night, the temperature being then taken at six o'clock next morning and at two-hourly intervals. Examination of the chest for the local reaction should begin at the same time, and be repeated at three- to four-hourly intervals until the presence or absence of local reaction is established. For the purpose of the test Koch's Old Tuberculin is usually employed. Some people being very sensitive to it, it is best to begin with a dose of only 0.0001 c.c., to which only very exceptionally is any response made. Should no reaction occur, the dose is increased ; 0.001, 0.003, 0.005, 0.007, 0.01, 0.1 c.c., being used at successive intervals of two or three days until a positive result is secured, as

is usually the case with the second or third of these doses in tuberculous cases. A negative result with the last of these doses is considered to be final so far as infection by the human type is concerned. If thought desirable, infection by the bovine type may be excluded by repetition of the test with bovine Old Tuberculin (P.T.). Some cases of advanced phthisis do not respond to the test, but these present little difficulty in diagnosis. It has also been stated that certain cases of syphilis have given a positive reaction, but against this it must be borne in mind that sufficient proof that these cases were not also infected somewhere by the tubercle bacillus has not been always forthcoming.

Contra-indications to use of the test are : (1) If the temperature rises above 98.6° in the axilla, or 99° F. in the mouth ; (2) if definite signs of tuberculosis be present, if tubercle bacilli be present in the sputum, or if there has been a recent attack of hæmoptysis ; (3) if there be grave renal or cardiac trouble ; (4) if the patient be subject to epileptic fits.

2. *Constitution of the Tubercle Bacillus and of the Tuberculins.*

A considerable amount of study has been devoted to the chemical composition of the tubercle bacillus, with the view of obtaining indications as to what constituents should be included in a tuberculin in order to secure the best immunizing effects.

Renon gives the following account of the products obtained by the treatment of the bacillus with various solvents :

Distilled water removes albumins.

A 10 per cent. solution of sodium chloride acting for twenty-four hours at 38° C. removes globulins.

Alcohol, ether, and chloroform remove the fatty envelope, the two former more especially that constituent which leads to caseation effects, the latter the one which induces sclerosis.

Strong acetic acid at 80° C. dissolves the bacillary casein, a para-nucleo-albumin, which is the essential protoplasmic substance, and when stained with carbol fuchsin strongly resists discoloration by means of acids, but yields more readily to absolute alcohol.

When the bacilli are grown in alkaline-glycerine-peptone broth, toxic products are found in the culture fluid; but whether these are exotoxins or endotoxins liberated by autolysis of the bacilli is not certain. The bodies of the bacilli themselves contain very toxic substances, as we have seen above; the main toxic effect would appear to be a local one upon the tissues surrounding an infected focus, the symptoms of general toxæmia being as a rule little in evidence.

The preparations of the tubercle bacillus are made either from the fluid medium in which the bacilli have grown, from the bodies of the bacilli themselves, or from a mixture of the fluid medium and of extractives from the bacilli. The more common ones are made as follows:

From the culture fluid—

1. T.O.A. is simply the fluid in which the bacteria of the human type have grown, unaltered in any way except that the bacillary bodies have been removed by filtration through a Chamberlain candle.

The corresponding preparation from the bovine strain is known as P.T.O., not P.T.O.A.

2. Vacuum tuberculin is T.O.A. which has been con-

centrated by evaporation at a low temperature in a partial vacuum to one-tenth its original bulk. Deny's tuberculin corresponds closely to this preparation. The corresponding bovine preparation is designated bovine vacuum tuberculin.

3. T., or Old Tuberculin, is prepared from the four to five weeks' old cultures of the human type bacillus in glycerine broth in the following way : The cultures are treated with steam for half an hour to insure sterility ; they are then placed in steam-heated vessels fitted with a vacuum apparatus, and evaporation is conducted at 70° C. until the volume is reduced by nine-tenths. Filtration through porcelain candles is then performed, the filtrate allowed to cool, and 0·5 per cent. phenol added. Sedimentation of indifferent substances is allowed to proceed in a cool place for several weeks ; these are removed by filtration, the clear filtrate now constituting Old Tuberculin, or T., which differs thus from T.O.A. and vacuum tuberculin, not only in the fact that concentration has been produced with the aid of heat, but also in that the bacilli have been partly extracted with hot steam, the albumin and some of the globulin of the bacillary bodies thus being taken into solution.

The corresponding bovine preparation is known as P.T.

From the bodies—

1. T.O. The bacilli are finely triturated and extracted with water until all the constituents soluble therein are removed ; this solution of the soluble constituents was designated T.O. by Koch, and regarded by him as of no therapeutic value. It is supposed to contain nothing but toxin. As we have already seen, the extracted substance is an albumin. (Note that P.T.O. is the bovine preparation corresponding to T.O.A., and not to T.O.,

as might be well imagined.) The bacillary residue, after the extraction with water is complete, is utilized for the preparation of T.R.

2. T.R. The triturated bacillary residue is alternately treated with water and centrifugalized; after each centrifugalization the supernatant fine suspension is pipetted off. These emulsions are finally bulked together, and concentrated by the aid of heat and 20 per cent. glycerine added to constitute T.R. The amount of solid matter in each cubic centimetre is derived from an initial 10 milligrammes of tubercle bacilli, and the concentration is conducted until 2 milligrammes of solid substance are present in the emulsion. T.R. is thus composed of such portions of the bacillus as are insoluble in water—*i.e.*, of some of the globulin, of the fatty envelope, and the essential protoplasmic casein or para-nucleo-albumin.

The corresponding bovine preparation is designated P.T.R.

3. Vacuum T.R. is precisely similar in method of preparation to T.R., except that the necessary concentration of the bulked suspensions is conducted in a vacuum instead of by the aid of heat.

4. B.E., or bacillary emulsion, is prepared by triturating the whole bacillary bodies, and emulsifying each 0.5 gramme of the powder with a mixture of 50 c.c. glycerine and 50 c.c. distilled water. Each cubic centimetre therefore contains 5 milligrammes of bacillary substance, from which nothing has been removed by the aid of solvents.

The corresponding bovine preparation is designated P.B.E.

5. S.B.E. Sensitized bacillary emulsion, or tuberculo-sero-vaccine, is prepared as follows: Bacilli of the

human type are collected on a filter, and thoroughly washed with normal salt solution. They are then placed in a suitable quantity of a specific tuberculosis immunizing serum derived from an animal which has been immunized with living human-type bacilli, and triturated by agitation with beads ; the disintegration of the bacilli is assisted by heating the mixture of bacilli and serum together at 37° C. for a long time. When the trituration of the bacilli is complete the mixture is centrifugalized, the sediment repeatedly washed with normal salt solution, and finally emulsified with 50 per cent. glycerine solution, 1 c.c. of the emulsion containing 5 milligrammes of solid matter. The idea of this preparation was that a fixation of the specific immune bodies, present in the serum of the immunized animal, should be effected with the tubercle bacilli. The idea does not seem to be realized in actual practice, despite the favourable reports of Citron.

6. Béraneck's tuberculin differs from other preparations in that it is composed not only of the toxins diffused into the culture medium, but also of substances extracted from the bacillary bodies by the aid of orthophosphoric acid. With the aim of keeping the product as free as possible from toxic but non-immunizing substances, the broth in which the bacilli are grown contains neither peptone nor albumose. When free growth has occurred the bacilli are removed by filtration, and an extract of the bacillary protein made with the aid of a 1 per cent. solution of orthophosphoric acid ; equal portions of this extract and of the culture medium which has previously been evaporated down at a low temperature *in vacuo* to a tenth of its bulk are mixed together to form the finished product. Béraneck claims that this preparation is not only as potent as any other preparation in stimulating

the formation of immune bodies, but that it is also much less toxic, so that more powerful immunizing effects can be produced without giving rise to undesirable reactions. Sahli supports this contention; but from the description of some of the reactions obtained in his cases, it would seem that its toxicity for tuberculous guinea-pigs is no measure of its toxicity for tuberculous human beings. Nevertheless, there is something to be said theoretically in its favour, and further clinical experience may confirm the claims made on its behalf.

3. Immunity against the Tubercle Bacillus and the Tuberculin Reaction.

One attack of tuberculosis does not seem to confer any immunity against another, but, on the contrary, rather to predispose to it—that is, if we except the immunity to subsequent infection by the human strain which appears to be conferred by an infection by the bovine strain. That general constitutional immunity, due probably to biochemical causes, exists is highly probable, but local immunity appears to be a most important defensive mechanism.

Phagocytosis, apparently, is a most important agency in the destruction of the bacilli, and is carried out almost entirely by the giant and endothelial cells. Whether the polymorphonuclear leucocytes play any part therein, except perhaps in cases where the bacilli have gained access to the general circulation, is very doubtful. Opsonin, partly of the thermostable variety, but chiefly of the thermolabile, can be demonstrated in the blood-serum; but whether sensitization thereby of the bacilli is necessary prior to phagocytosis by the giant and endothelial cells has not been determined.

Wassermann and others have demonstrated the presence of antibodies in those who have been immunized with tuberculin ; no bactericidin or antitoxin has been demonstrated. Lysin and agglutinin are frequently present, but are sometimes absent even in cases that are doing well.

The Tuberculin Reaction.—The exact manner in which the tissues of the tuberculous subject react to an inoculation of tuberculin has been the source of much argument, and the matter of much investigation. The chief cause of dispute has been the delay which occurs in the response to the inoculation, a delay in no wise peculiar to tuberculin, but which is likewise experienced when any other vaccine is employed.

The recent work of Wassermann, Wolff-Eisner, Rosenau, Vaughan and Wheeler, and of others, has tended to show that in the tuberculous individual the cells are sensitized by the action of the infecting bacillus and its products, and that when tuberculin is injected it is split into a toxic and a non-toxic portion, the former of these being rapidly bound by the sensitized cells, and giving rise to the tuberculin reaction. In non-tuberculous individuals the condition of hypersensitiveness of the cells does not exist ; when tuberculin is introduced into the tissues the splitting process into the two constituents is slow, the combination of cell and toxin either does not occur at all, or only to a slight extent, and the toxin is rapidly destroyed or discharged. When hypersensitiveness exists certain changes are produced in the cell whereby they are enabled to break up the tuberculin, and combine with it with great rapidity.

Meyer and Schmitz have attempted to determine what the substance is that reacts with the tuberculin. They infected rabbits with bovine tuberculosis, bled them, and

allowed the serum to stand for twenty-four hours mixed with bovine bacilli, and then injected it into healthy animals; these became ill, with considerable rises of temperature and other constitutional disturbances. The serum from animals with advanced tuberculosis was found to answer best, and a still stronger reaction was obtained when washed blood-corpuscles were used instead of serum. Also, when the washed blood cells of tuberculous animals were allowed to react with tuberculin and saline solution, the mixture centrifugalized, and the saline solution alone injected into healthy animals, a reaction was still obtained; this, however, was never the case when the blood cells or serum of healthy animals were employed. Heating above 65° C. did not destroy the bodies that gave rise to the reaction.

It would thus appear that in the blood of infected individuals there circulates a substance, combined for the greater part with the red blood cells, which combines with tuberculin, and is then capable of producing a febrile reaction and other symptoms of disease in healthy subjects.

4. *Choice of Cases for Tuberculin Treatment, Choice of Tuberculin, Control of Dosage and Intervals—Results.*

The decision as to whether a given case of pulmonary tuberculosis is or is not suited for tuberculin treatment is a problem by no means devoid of difficulty. The chaotic state into which the minds of all were thrown in the first place by the failures and accidents encountered under the original system of dosage advocated by Koch, and in the second place by the disappointing results obtained by the application of Wright's principles to the dosage of tuberculin in cases of pulmonary phthisis.

has done much to impede progress. The better understanding that has been recently attained of the nature of the tuberculin reaction and of the means whereby the body acquires immunity against the tuberculo-toxin on the one hand, and the bacilli themselves on the other hand, is serving to explain why it is that the small and infrequent dosage, so well adapted to the treatment of strictly localized and surgical tuberculosis, is ill-adapted to the widely diffuse pulmonary form. In the former variety autotoxæmic disturbances are slight, and there is no necessity, therefore, to overcome sensitiveness, and establish a high degree of tolerance to the tuberculin toxin. In the latter condition, the autotoxæmic disturbances, as evidenced by irregular pyrexia, quickened pulse-rate, and bad general conditions, are considerable; sensitiveness to the tuberculin toxin is then very high, and can be overcome only by establishing a high degree of tolerance by the administration of such doses of tuberculin as will rapidly nullify the administration from within of irregular dosages at irregular intervals. It is at the same time obvious that the difficulty of establishing a satisfactory degree of toxin immunity will be minimized by the adequate control of the inoculations of auto-toxins, and that these latter may be so uncontrollable and so considerable as to render impossible the task of overwhelming their irregular impulses by the well-ordered waves of immunity set up in response to stimulation with regular and adequate doses of tuberculin. The slight discord introduced into the performance of a piece of music by a flautist in a band may easily be masked beneath the greater volume of harmony emitted by the brass, but not all the sweet tones of flute and clarinet and harp will mask the blatant discords of trombone and

double bass. Hence it is that phthisical cases in whom autoinoculation effects are marked are unsuited to tuberculin treatment, and that the control of these by rigid rest and other measures becomes a matter of such urgency and importance.

The statement is frequently made that cases of mixed infection are unsuited to tuberculin treatment; this is a very misleading statement. That cases of mixed infection are unsuited as a rule to tuberculin treatment is due, not to the fact that they are cases of mixed infection, but to the fact that autoinoculation effects are as a rule marked, and that, moreover, it is almost impossible to separate the autoinoculation effects referable to the mixed infection from those referable to the tuberculous infection. The fact that mixed infection gives rise to increased cough and respiratory efforts has also to be borne in mind. These cases, therefore, are not intrinsically unsuited to tuberculin therapy; they are so only temporarily, and until the mixed infection has been dealt with adequately according to the methods outlined in an earlier part of this chapter. There is a third class of case in which tuberculin treatment appears to be contra-indicated—*i.e.*, that class in which sensitiveness to tuberculo-toxin is so great and tolerance so low that the administration of doses of tuberculin sufficiently great to overcome these disabilities is rendered impossible by the grave constitutional disturbances thereby engendered. To this it may be urged that it is only the treatment of such cases by massive doses of tuberculin that is contra-indicated, and that such cases are well suited to the small and infrequent dosages advocated by Wright. This may indeed be true, but in practice I have found it otherwise; small infrequent doses do nothing to diminish sensitiveness and increase toler-

ance to the tuberculin toxin, but have rather the contrary effect; and the better practice in these cases is probably to place them under the best possible conditions, and leave them to establish tolerance and diminish sensitiveness by means of controlled auto-inoculations. This class of case is by no means common, and is to be expected most among the very early closed cases; occasionally such a condition is temporarily established by the administration of a diagnostic dose of tuberculin. Finally, in the following forms of the disease tuberculin treatment is liable to do more harm than good: (a) In the broncho-pneumonic form; (b) in those where caseation is marked, for softening, cavitation, and perhaps serious hæmorrhage, and dissemination may be induced; (c) in those where the disease is very widespread, especially if the pulse be very rapid—*i.e.*, 120 or over—a very rapid pulse is a much stronger contra-indication than is a high temperature, for the latter is usually much easier of control than is the former; (d) serious complications. On the other hand, hæmoptysis, slight complications, and pregnancy do not contra-indicate tuberculin treatment.

Choice of Tuberculin.—With the general view that all tuberculins produce the same effect, and act in a similar manner, and that one preparation brings about as good results as any other, I cannot at all agree. While it is probably true that the use of each and every tuberculin tends to establish tolerance and diminish sensitiveness, it must surely be admitted that the use of such preparations as contain toxins only can never suffice to bring about an antibacterial immunity. Tolerance to tuberculo-toxin will enable the sufferer to go about his daily duties even though he continue to expectorate great

numbers of bacilli, and perhaps suffice to minimize greatly the ill-results which would otherwise inevitably attend upon the bacterial infection, but it can never lead to its extinction; this only a high antibacterial immunity can bring about. Granted that we know but little on this subject of antibacterial immunity, it may yet be reasonably deduced from analogy with every other variety of organism that the administration of the bacterial bodies and their essential protoplasm is the best available means for inducing its increase. When, therefore, toxæmic symptoms predominate, it would appear to be most rational to endeavour to stimulate antitoxin formation by the administration of such toxic products as Old Tuberculin, P.T.O., or Bouillon Filtrate; in the more severe cases beginning with the mildest preparation—viz., the P.T.O.—and concluding with the most potent, the Old Tuberculin. In very sensitive cases, however, the use of the bacillary emulsion may, owing to its very slow absorption, possess distinct advantages. When, on the contrary, toxæmic symptoms are in abeyance, it would appear to be more reasonable, perhaps after a preliminary course with a toxin preparation such as Old Tuberculin, to endeavour to establish a true antibacterial immunity with the aid of T.R. and bacillary emulsion. Whatever preparation is utilized, I feel sure that the autogenous preparation is necessarily the most suited to the case, and the ease with which the tubercle bacillus can now be isolated from the sputum will facilitate greatly the experimental confirmation of this view. In default of the autogenous tuberculin, a polyvalent stock preparation is next to be recommended, while the combination of human and bovine strains, which I first advocated three years ago, appears to possess distinct advantages.

The Control of Dosage and Interval.—(1) According to Wright's method ; (2) according to Koch's method, modified according to more recent experiences.

1. In Wright's method, as we have already seen, the object is to give a series of independent immunizing stimuli, whereby the general well-being is improved without any regard being paid to increase of tolerance or diminution of sensitiveness. If the method be conducted in its entirety, the control of dosage and interval is by means of determinations of the opsonic index, the aim being to employ such doses as will induce the maximum rise of index, and will maintain it at a high level for the longest possible time, reinoculation being performed as soon as the decline of index sets in, and increment of dosage being made when the old dose no longer proves efficient in these directions. The initial dose of any tuberculin preparation usually employed in this method varies from 0·000001 c.c. to 0·00001 c.c., and only exceptionally is it finally raised above 0·0001 c.c. to 0·0005 c.c. The interval between the administrations varies from ten to fourteen days.

Occasionally the method is employed more empirically, the guidance of temperature chart, general condition, and past clinical experience, being substituted for that of index. As we have already seen, this system of small infrequent dosage is admirably adapted for the treatment of localized and surgical tuberculosis, but the general consensus of opinion now is that it is ill-adapted for the treatment of pulmonary tuberculosis, and is accordingly being more and more discarded in favour of Koch's original method suitably modified.

2. *The Method of Immunization according to Koch, also known as the Intensive Method.*—In this method the

aim is to train the tissues to be able to cope with such doses of tuberculo-toxin as are liberated from the infected foci without evincing signs of pronounced constitutional disturbance. In order to achieve this end tuberculin is administered at short intervals in rapidly increasing doses, for this has been found to be the only way in which hypersensitiveness can be overcome and tolerance induced. The cure of the focal lesions is left to natural processes, these being merely stimulated to increased action by the hyperæmic condition there induced by the inoculations.

Some authorities there are who endeavour to achieve the desired end by so adjusting their stimuli that constitutional disturbances are avoided completely if possible; others adjust their stimuli so as to produce such disturbances, and regard these as evidences of efficient dosage; others, again, adjust their stimuli without any regard to the production or not of constitutional disturbances, aiming chiefly at being able to administer the highest possible dose of tuberculin in the shortest possible time. It is quite outside the scope of this work to go into these various methods; the one most in favour is that whereby the dosage is made the highest possible that will just avoid the production of marked constitutional disturbances. Whatever the preparation of tuberculin employed—and some prefer to employ Old Tuberculin throughout, others T.R., or B.E., or Béraneck's tuberculin throughout, while others, again, prefer to employ P.T.O., P.T., and Old Tuberculin in sequence—the initial dose is quite small. Thus, Denys and Wolff-Eisner begin with not more than 0.000001 c.c., Aufrecht with 0.000025 c.c., Bandelier and Röpke with 0.000001 to 0.0001 c.c. of Old Tuberculin, Rothschild with 0.0000001 c.c., Neumann with 0.000005 c.c., Krause with 0.00002 c.c., Möller with

0·00001 c.c., Bandelier and Röpke with 0·00002 to 0·0002 c.c., and Römisch with 0·0002 c.c. of T.R. or B.E. In three or four days the second dose is given, different authorities making different increments on the initial dose ; thus most use a double dose, but Bandelier and Röpke use one increased by half, and Neumann makes an increment of one-third only. Thereafter different scales are employed ; some use the progression, 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 20, 30, and so on, wherein there is a sudden marked increase after each series of ten inoculations ; others use a progression such as, 1, 1·5, 2, 3, 4, 5, 6, 8, 10, 15, 20, and so on ; while Bandelier and Röpke advise 1, 1·5, 2, 3, 5, 7, 10, 15, 20, etc. Whatever the notation employed for estimating the appropriate series of dosage, nearly all authorities who follow the system of avoiding reactions adopt the following principle when a reaction is produced ; they wait till all signs of the reaction have passed off, which varies from three to seven days, and then begin again, either with the dose which last failed to produce a reaction, or with one of half this amount, and then increase as before.

As regards the final dosage, which in the absence of a reaction thereto is regarded as demonstrating that a condition of full tolerance has been attained, authorities slightly differ ; 1 c.c. of the undiluted tuberculin is the limit fixed by most, but 0·1 c.c. is regarded as sufficient by many. These latter, of whom Petruschky is one of the chief advocates, alternate periods of treatment for three months, and rest from treatment for three months. After the maximum has been attained, the treatment is discontinued for three months, and then begun again *ab initio*, three or four such courses being administered whenever possible.

All these authorities unite in disregarding reactions at

the foci of disease, and state that the dosage which will produce a general reaction is less than the dosage which will produce a focal reaction of such magnitude that it can be observed. In this I unhesitatingly state that they are in entire error. If sufficient care is taken to observe and record with accuracy the clinical signs in the chest before the administration of such a dose of tuberculin as will produce none but the slightest possible signs of a general reaction, and these observations are continued at frequent intervals, such as six, twelve, twenty-four, and forty-eight hours, after the inoculations, I am certain that in all but a very small percentage of cases marked changes in the physical signs can be detected, changes precisely similar in character, if less in degree, than those already described on pp. 399-406, as being produced in response to an inoculation with an efficient dosage of a vaccine of catarrhal organisms, or of one corresponding to the organisms constituting the mixed infection. I would maintain that herein lies by far the best, easiest, and most reliable guidance to the appropriate dosage and intervals. Raised tolerance and diminished sensitiveness to tuberculo-toxin are desirable objectives, but they are not the real objective that we should have in mind. This is, firstly, the improvement of the general condition ; secondly, the improvement of the focal condition ; thirdly, the extinction of the infection ; and that scheme of dosage is obviously the best which produces the greatest amelioration in the focal condition, all other things being equal. Surely it is only logical, then, to claim that the best basis upon which to found a scheme of dosage is that built upon the changes produced at the foci of disease. It is on such lines that I now treat all my phthisical patients, and the principle I have adopted is as follows :

Begin with a very minute dose of that tuberculin which seems best adapted to the case (*vide* p. 427). By a very minute dose I mean 0·00001 c.c. for apyrexial cases, and 0·000002 to 0·000005 c.c. for pyrexial cases. The effect of this inoculation is closely watched and recorded. If no reaction or improvement occurs within three days, the initial dose is repeated; if, again, no reaction or change within three days, double the initial dose is given, and so on. Once a dose produces a focal reaction—and I have never yet seen a dosage which produced a general reaction fail to produce a focal one also—close observation is kept upon the altered physical signs. It may be stated as an axiom that in a case capable of making improvement, any dosage which will within twenty-four hours produce a reaction at the foci of disease, as evidenced by apparent increase of the involved area, increased moisture of the sounds, or multiplication of their number, will also, after a variable period—it may be one, two, three, or more days—likewise induce a more than corresponding amelioration in the physical signs, so that there will be a time when the focal condition is better than it was before that inoculation was performed. After a further variable period—it may be of one, two, three, or more days—retrogression will begin, and this is the signal for an immediate reinoculation. Under this system, which I would maintain is the most logical and scientific one yet devised, if unfortunately the one calling for the most care and attention on the part of the doctor, increase of dosage is indicated only by failure of production of an immunizing response at the focus of disease, and may be made according to the progression, 1, 1·5, 2, 3, 5, 7, 10. Occasionally a focal reaction of the following type is produced: Instead of increase in the area of apparent involvement and of the

moisture of the sounds, there is a diminution in these directions within twelve to twenty-four hours, either with or without the production of a slight general reaction. This is to be regarded as indication of a minimal efficient dosage, and of the advisability of an increase being made therein at the next administration.

Only very rarely, indeed, have I found a dosage produce a general reaction, and at the same time fail to produce a focal one. On one occasion a change to B.E. from Old Tuberculin overcame the difficulty; on another occasion I could find no scheme of dosage that would suit the patient. I found it impossible to increase the dose of Old Tuberculin beyond 0.00002 c.c. without giving rise to marked general reaction and considerable constitutional upset, and decided that it would be wise to discontinue tuberculin treatment for a time, and then recommence with 0.000001 c.c. B.E.

The one thing above all which should always be borne in mind is that whatever the system to which one may incline, whatever the scheme marked out for the treatment of any case, the man remains the prime consideration and not the scheme, and that when events are not taking the desired course, the one thing to do is to reconsider the case minutely, and endeavour to learn in what essential particulars modifications may be required.

5. *Autoinoculation in Phthisis.*

To Marcus Paterson is entirely due the credit of demonstrating the great value of the autoinoculation method of treatment in pulmonary tuberculosis, and to those who are interested in the method, and would learn how to apply it and what it can achieve, I would advise the perusal of his comprehensive monograph on the subject.

The facts bearing on the method are as follows :

1. That the irregular pyrexias of pulmonary tuberculosis are due to excessive and ill-ordered autoinoculations, with tuberculo-toxin derived from the infected foci.

2. That these can often only be controlled by the most absolute, or so-called ' typhoid,' rest.

3. That the reparative processes and the acquirement of a high degree of tolerance to tuberculo-toxin may be greatly assisted by the induction of carefully ordered auto-inoculations by means of graduated exercise and labour these autoinoculations being induced after adequate control of their spontaneous production has been gained, if necessary, by the application of absolute rest.

That the method is one of extreme value may be at once admitted, but it has its disadvantages, among which may be mentioned—

1. It can only be carried out thoroughly in institutions where the patients are well under control, and where facilities exist for the provision of labour of various kinds and various grades.

2. That, strictly, it is only applicable to cases from which mixed infection is absent, for just as autoinoculation is induced with tuberculo-toxin, so autoinoculation is induced with the products of the mixed infection, and no means are available of ascertaining how much of the autoinoculatory effects, which are measured by means of the temperature and pulse charts, are due to the tuberculo-toxin, and how much to the latter toxins.

3. That whereas at the beginning of treatment, when the induction of only small autoinoculations is required, a practically unlimited amount of autoinoculation can be induced, as the case proceeds to ' arrest ' of the infective processes, and the tissues require large stimuli to produce

immunizing effects, small stimuli only are capable of production. Paterson's contention is that if signs of autointoxication cannot be induced by a day's hard manual labour, there can be little danger in allowing such a patient to return to his occupation. This would be true were it the case that extinction of the infection and the impossibility of producing autoinoculation effects were synonymous ; this, unfortunately, is not the case, and the return of such an individual to hard work in unfavourable surroundings is extremely apt to lead to speedy relapse. It is somewhat unfortunate that Paterson should be prepared to regard the disease as arrested in an individual who continues to expectorate tubercle bacilli.

Personally, I think that there is a great field for the application of the valuable lessons which Paterson has learnt and teaches. There is no tuberculin so well adapted to the treatment of a case as that formed by the affected individual for himself, but I think the wisest procedure would be as follows :

1. Control autoinoculations by rest, absolute if required.
2. Eliminate mixed infections by means of autogenous vaccines.
3. Raise tolerance by a short course of Old Tuberculin.
4. Proceed to autoinoculate by means of graduated exercise and work.
5. When these stimuli fail to produce any reaction, recommence tuberculin treatment, perhaps best with the bacillary emulsion ; employ the intensive method, and proceed to massive doses, and so endeavour to raise antibacterial as well as antitoxic immunity, and eliminate the bacterial infection.

This elaborate method might well prove to be the best yet devised for the treatment of pulmonary tuberculosis.

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